CONTROL MONITOR: A MATHEMATICAL MODEL BASED COMPUTER SYSTEM TO ASSIST THE CONTROL OF INSULIN DEPENDENT DIABETES

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Abstract

The purpose of this project has been to develop a computer system to assist the Insulin Dependent Diabetes Mellitus patient. The idea being to obtain more accurate and dynamic control of the blood glucose level by using a mathematical model which can be used to investigate variations in food and insulin intake in order to keep the blood glucose level within the required limits.

The feasibility of such a system being useful to diabetics has been due to the developments that have been made in the field of electronics, especially microprocessors. These have led to the development of the home blood glucose testing machines, which allow frequent and accurate testing of blood glucose levels. The model requires these for input, since such a model could not be expected to extrapolate blood glucose levels over long periods of time. The availability of the personal computer has put the computing power required for the implementation of such a model within the reach of an increasing number of people.

PREFACE

I have had insulin dependent diabetes since August 1969. I was on a single daily dose of long acting insulin from then until 1985. In October 1985, following a change of consultant, I started a basal/bolus regime of a long acting dose of Ultratard plus three meal time short acting doses of Actrapid. I also purchased my first home blood glucose testing machine the same week as changing to multiple insulin doses. I completed a degree in computer science at the end of 1985. These factors led me to come up with the idea that I could develop a numerical model to optimise blood glucose control using the blood glucose readings, insulin dose data and food intake measurements.

After formulating a mathematical representation for blood glucose extrapolation, I developed a Pascal program to collect the required information and implement the model.

A few modifications and additions have been made to the program over the years since the original implementation. Graphical output was added in 1992. As with most programs written in the 1980's the code developed for this project used dates with two digits for the year, hence suffered from the "Y2K" problem. This required some updating before the end of 1999. Dates

were changed from 6 digit to 8 digit format, and some date handling routines modified. I started using Novorapid, a new "designer insulin", in 2003 and so added an insulin type implemented by the program to handle the different reaction curve of this type of insulin.

Over the past 20 years, I have found the system to be a very useful aid to assist with the control of my diabetes.

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Updates: A function for insulin detemir was added in November 2007.

Contents

1 Introduction **11**

1.1 Overview 11

1.2 Applications of Computers in Diabetes Management 13

1.2.1 Data Storage 13

1.2.2 Drawing Graphs of Results 14

1.2.3 Mathematical Modelling 14

1.2.4 Education 14

1.3 Personal Computers 15

1.4 Project Objectives 15

1.4.1 Optimize Control 15

1.4.2 Provide Support for Self-Monitoring 16

1.4.3 Assess Insulin Requirements 17

1.4.4 Apply Computers to Patient Education 17

2 Computers in Medicine **18**

2.1 Administration of Patient Records 18

2.2 Medical Imaging 18

2.3 Artificial Intelligence and Expert Systems 19

3 The Physiology of Diabetes **21**

3.1 Definitions 21

3.1.1 Blood Glucose Level 21

3.1.2 Hypoglycaemia 22

3.1.3 Hyperglycaemia 22

3.1.4 Control 22

3.2 Common Abbreviations 22

3.3 Insulin 23

3.3.1 The Islets of Langerhans 23

3.4 Metabolic Function of Insulin 24

3.5 Factors Affecting Blood Glucose Concentration 26

3.5.1 The Effect of Food on Blood Glucose Level 26

3.5.2 The Effect of Insulin on Blood Glucose Level 27

3.5.3 Exercise 28

3.5.4 Metabolic Functions Not Requiring Insulin 28

3.5.5 Glucose Excretion by the Kidneys 29

3.5.6 Liver Function 29

3.5.7 The Symogyi Effect 29

3.5.8 The Dawn Phenomenon 30

4 The Diabetes Control Problem **31**

4.1 Diabetes Complications 31

4.2 Treatment 32

4.3 Insulin Therapy 34

4.3.1 Intensive Insulin Therapy 36

4.3.2 Insulin Dose Adjustment 37

4.4 Exercise 37

4.5 Education 37

4.6 Blood Glucose Metrics 38

4.7 Diet 39

5 The Mathematical Model **40**

5.1 The Model Equation 40

5.2 Insulin Action Profiles 41

5.3 Approximation of Insulin Reaction Curves 42

5.3.1 Actrapid 43

5.3.2 Ultratard 46

5.3.3 Novorapid 48

5.3.4 Insulatard 49

5.3.5 Protaphane 49

5.3.6 Detemir 50

5.4 The Food Equation 51

5.5 The Effect of Exercise on Blood Glucose Level 52

5.6 Hepatic Glucose Production 52

5.7 Urinary Excretion of Glucose 53

5.8 The Dawn Effect 54

5.9 Insulin Resistance 54

5.10 The Somogyi Effect 55

5.11 Approximations, Simplifications and Model Accuracy 55

5.12 The Model Parameter Matrix 56

5.13 Corrected Blood Glucose Extrapolation 58

6 Implementation **60**

6.1 Source Code Structure 61

6.1.1 Control.pas 61

6.1.2 Utilmod.pas 61

6.1.3 Menu.pas 61

6.1.4 DataUnit.pas 61

6.1.5 Insulin.pas 63

6.1.6 Foods.pas 63

6.1.7 Model.pas 63

6.1.8 Graphix.pas 64

6.1.9 TxtPlot.pas 64

6.2 The Model Parameter Matrix 64

7 Functions of The Control Monitor System **65**

7.1 Running the System 66

7.2 Menu Options 66

7.3 Producing Reports 70

8 Results **75**

8.1 Measures of Performance of the System 75

8.2 Blood Glucose Value Extrapolation 76

8.3 HbA1c 79

8.4 Discussion 81

9 Some Other Diabetes Related Systems and their Impact on Diabetes Care **83**

9.1 Origin of Ideas and Groundwork in this Field: 1981 - 1990 . . 84

9.1.1 Home Blood Glucose Monitors 84

9.1.2 Skylers Algorithms 84

9.1.3 BCMC 84

9.1.4 Early Publications on the Subject of Model Based Systems 85

9.2 Early Systems: 1985 - 1999 86

9.2.1 Pernick and Rodbard's Monitoring and Dosage Adjustment System 86

9.2.2 AIDA 87
9.2.3 DIAS 87
9.2.4 DIABLOG 88
9.2.5 Prototypical Systems - Ideas and Concepts 89
9.3 Recent Systems: 2000 onwards 89
9.3.1 HumaLink 89
9.3.2 Librae Body Double 90
9.4 Benefits of using the Systems 91
9.5 Problems, Issues and Limitations 92
9.6 Comparison of the Systems 93
9.6.1 Historical Perspective and Originality of Concepts . . . 93
9.6.2 System Viability and Survival Periods 94
9.6.3 Range of Platforms Supported 94

10 Conclusions **96**

References **98**

Acknowledgements **102**

A Example Report Output **103**

B Project Proposal **111**

C Source Code **115**

Chapter 1

Introduction

1.1 Overview

The work described here involves the application of numerical methods and computers in the field of medicine, and documents the implementation of the Control Monitor system. The aim of this project has been to develop a practical computer based system that can be used to aid the problem of blood glucose level control in (Type I) Diabetes.

Insulin Dependent Diabetes Mellitus (IDDM), also known as Type I Diabetes, is a condition which results when the pancreas fails to produce insulin. The main symptom of diabetes is an elevated level of glucose in the blood. The body is unable to use this glucose for energy or store it away, since without insulin, it cannot enter the cells, and hence it builds up in the blood. Diabetes is a chronic, incurable disease. It is also a condition of significant proportions.

There are an estimated 246 million adults with diabetes worldwide, with about 15% of people with diabetes having Type I (www.idf.org), and there are an estimated 1.27 million people with Type I diabetes in Europe. (Bellazzi, 2003) Data available estimates that in 1997, the prevalence rate for Type I Diabetes in children under 15 years of age was 8.3 per 10 000 in the United States of America, and 6.4 per 10 000 in Canada. (Barcelo and Rajpathak, 2001)

IDDM is treated by insulin injection, and the timing and quantity of the doses are critical factors in successful treatment.

The aim of developing this system has been to enable more accurate and dynamic control of the blood glucose levels. This is done by the computer analyzing the data using a mathematical model of the situation which extrapolates the blood glucose level from the supplied data, and thus allowing variations in food and insulin intake to be made to keep the level within the specified limits. Due to the nature of the problem, the construction of a straight mathematical model giving a high degree of accuracy in extrapolation is not very feasible. There is a large amount of uncertainty introduced by outside factors, and the general behaviour of biological system., However, it should be noted that the system can still be useful even if the mathematical model does not provide a high level of accuracy.

The feasibility of such a system being useful to diabetics is due to developments that have been made in the field of microprocessors in recent years. These have led to the development of the home blood glucose testing machines, which allow regular and accurate testing of blood glucose levels. The

availability of the personal computer has put the computing power required for the implementation of such a model within the reach of many people. The ideal situation would be for the diabetic to know their blood glucose level at all times. The home blood glucose measuring machine allows the value to be determined a number of times during the day. The function of this system is to fill in the gaps between those readings. It could be possible for a diabetic to perform four tests on a particular day, and find them all to be in range, when the level has in fact been going up and down, and at times has been above and below acceptable values. The system is able to show this by filling in those gaps between the readings.

1.2 Applications of Computers in Diabetes Management

There are a number of ways in which computers can be applied to aid the task of diabetes care.

1.2.1 Data Storage

All diabetics are encouraged to keep records of insulin doses and test results. There are advantages to doing this using a computer.

1.2.2 Drawing Graphs of Results

Plotting graphs of blood glucose readings is useful in that it gives a visual representation of the situation, which can improve understanding.

1.2.3 Mathematical Modelling

Here the computer is used to perform numerical manipulation of the data available in order to predict what is going to happen to the blood glucose levels over a period of time.

1.2.4 Education

A major use of computers is the storage and retrieval of information. Often this information can be used in some aspect of teaching. The success of therapy to improve blood glucose control relies on patient behaviour modification via education and guidance (Jackson et al, 2006). This is a process that IT systems can be applied to. Software could be used to teach diabetics about the disease. Computers can be used in diabetes education in an interactive manner, the sessions being based on the data input by the patient.

1.3 Personal Computers

The use of personal computers has increased hugely over the past 20 years. The system described here was developed during the mid-1980's, the early years of the rise of the IBM PC and compatibles. The proportion of the population in the 1980's with home computers was small. In the 21st Century, the PC has become just another appliance and large numbers of people have access to one either at home, at work, or both. While at the time this system was first developed the number of people it could have benefitted may have been considerable, the potential user base for a system such as this one is now very large.

1.4 Project Objectives

The objectives have been to apply computers in diabetes care in the following ways:

1.4.1 Optimize Control

The objective here is to obtain more accurate and dynamic control by having the computer extrapolate the blood glucose level by simulating the situation using the supplied data, knowledge about the physiology and mathematical modelling. The system can then be used to suggest variations in food and insulin intake in order to improve the level of the control. Obtaining the high-

est level of control possible is important in that it has the effect of reducing the complications associated with diabetes. While considered to be the case for many years, this fact has now been shown by the DCCT. (DCCT, 1993)

1.4.2 Provide Support for Self-Monitoring

The objective of this project has been to develop a practical computer based system that can be used by diabetics in order to improve their levels of control. Unlike many other medical conditions, the patient is central in the treatment of diabetes. The proportion of time for which health care providers are actively providing care is small compared to the time spent by the patient in this task (Gorman, 2001). Montagnana et al (2009) state that blood glucose self-monitoring is an integral part of diabetes care, and that patients on intensive insulin therapy should check their blood glucose level at least three times per day. Control is achieved through monitoring of blood glucose values, and adjusting the treatment when the test results indicate that adjustment is required. Any tool which assists in the task can be of benefit to the patient. A computer can be used in a number of ways to aid the patient in the task of self monitoring. All diabetics are encouraged to keep records of insulin doses and test results, and this can be done effectively using a computer. Once the data is stored on a computer it can be analyzed and used in a number of ways, including the production of statistical information about food intake, insulin doses and blood glucose readings, and plotting graphs of blood glucose readings. The production of graphical output is useful in that a visual representation of the data can enhance understanding

and often highlights trends in the blood glucose level fluctuation. The core component of this system is the predictive mathematical model. This has the aim of allowing blood glucose levels to be calculated at future points in time after recent blood glucose readings. The system has been implemented to allow use of the model to produce a useful tool for therapy changes by showing blood glucose fluctuation when alterations in food intake, insulin doses and exercise levels are made to the values input into the system.

1.4.3 Assess Insulin Requirements

Insulin dosage is worked out mainly on a trial and error basis. The model provides a quantitative tool to calculate the required insulin doses for given input values of food.

1.4.4 Apply Computers to Patient Education

Education is important in that it promotes compliance and motivation. Knowledge and understanding are an important part of treatment. The system shows how insulin, food and exercise affect blood glucose levels, as well as helping to organise the data so that results can be better understood.

Chapter 2

Computers in Medicine

2.1 Administration of Patient Records

Computerised systems are being used widely replacing paper based records. these have a number of advantages. Types of system include Electronic Patient Records (EPR), Hospital Information Systems (HIS) and Picture Archiving and Communication Systems (PACS).

2.2 Medical Imaging

Digital Radiology has a number of advantages over conventional film based methods. These include enhancement of processing that can be done with the images, and more efficient transmission and storage of the images.

The radiological applications of CT scanning and MRI also rely heavily on computing. Both of these imaging techniques require extensive numerical processing to reconstruct images from the signals detected. In the case of MRI, the Fourier Transform is used, which is a computationally intensive operation.

2.3 Artificial Intelligence and Expert Systems

According to Yazdani and Narayanan (1984), there is no clear definition of what Artificial Intelligence (AI) is. It can be loosely described as making machines perform tasks which require intelligence. One of the main aims of AI is to make machines more useful.

An expert system is a computer program which embodies expert knowledge on a particular domain. Expert systems is the branch of AI that has had the most practical success, many expert systems being in scientific and commercial use.

A large number of the early expert system were in the field of medicine. Some are diagnostic, while others deal with areas of medical management. A well-known successful medical expert system is MYCIN, which was constructed to assist in the diagnosis of infectious blood diseases. (Jackson, 1984)

As well as diagnosis, medical management is also an area applicable to expert systems. Patients with well-established diagnosis can present difficult and challenging management problems. Management is a long-term pro-

cess requiring intermittent attention of the physician. A computer system is useful here since it remembers all the details from one encounter to another.

Chapter 3

The Physiology of Diabetes

3.1 Definitions

3.1.1 Blood Glucose Level

The concentration of glucose in the blood, this is expressed either in mg/dl, or mmol/l.

1 mmol/l is equivalent to 18 mg/dl.

Normal blood glucose level is considered to be within a range between 80 and 160 mg/dl.

(4.4mmol/l - 8.9mmol/l)

(Augstein et al, 2007)

3.1.2 Hypoglycaemia

Blood glucose level below the normal range.

3.1.3 Hyperglycaemia

Blood glucose level above the normal range.

3.1.4 Control

The term control in the treatment of diabetes refers to the the attempt to achieve normal physiology. This is done by regulating food and insulin intake, and is assessed by taking blood glucose readings. Control is more than keeping glucose levels normal - adequate insulin must be available at all times, glucose must be stored and used properly, and body cells need to be properly nourished. (Krall & Beaser, 1989)

3.2 Common Abbreviations

IDDM Insulin Dependent Diabetes Mellitus

NIDDM Non-Insulin Dependent Diabetes Mellitus

SMBG Self-Monitored Blood Glucose

HbA1c Glycosylated Haemoglobin

3.3 Insulin

Insulin is a hormone, produced by the pancreas, which is used by the body in the metabolism of glucose. Hormones are substances that carry information (or messages) to cells. Insulin is a hormone that allows glucose to enter the cells.

3.3.1 The Islets of Langerhans

These are endochrine glands found in the pancreas. Endocrine glands are structures which make hormones and release them directly into the blood-stream. The Islets of Langerhans contain alpha, beta and delta cells. Beta cells measure blood glucose value, manufacture and release insulin. Alpha cells make glucagon, this is a hormone which raises the blood glucose level. Delta cells make somatostatin, this blocks glucagon and the anterior pituitary growth hormone. The pancreas also has the exocrine function of making enzymes.

Failure of the pancreas to produce insulin causes the condition known as Type I Diabetes or Insulin Dependent Diabetes Mellitus (IDDM). In the absence of insulin, the glucose is not able to be stored by the liver, or enter the cells. This results in the body not being able to utilize glucose for energy. Glucose produced from food intake remains in the blood, where its concentration rises above the normal levels, resulting in hyperglycaemia.
Type II Diabetes is a similar condition, in which insulin is produced by the

body, but is not effective. This is also known as Non-insulin Dependent Diabetes Mellitus (NIDDM). (Krall and Beaser, 1989)

3.4 Metabolic Function of Insulin

The function of insulin is in the process of the metabolism of glucose, it is the key that allows glucose to enter cells where it can be used for energy, and also signals the liver to convert glucose to glycogen for storage. Insulin is required for the entry of glucose, amino acids and fats into the cells, so that they can be utilized as fuel. The beta cells are continuously measuring the blood glucose level and releasing insulin as necessary in order to keep it at the correct level. After intake of carbohydrate, as soon as the blood glucose level starts to rise insulin will be released in order to counteract this.

The body requires fuel and building materials from food. The body uses three main fuels: glucose from carbohydrates, amino acids from proteins and fatty acids from fats. Approximate energy requirement is 25 calories per Kg (of ideal weight) per day. With increased activity the body requires more calories, but not more insulin.

Carbohydrates are broken down into glucose which then enters the blood. That which is not required for energy must be stored. Two ways it is stored are as glycogen and adipose tissue. Using insulin, the liver cells take up glucose and transform it to glycogen. This is stored in the liver and muscles. It is a quick form of energy, its release is stimulated by adrenalin and glucagon.

Insulin is also used to convert excess glucose into adipose tissue (fat). Insulin reacts with receptors on the surface of the cells and this causes events to take place which allow glucose to enter the cell. Protein is broken down into amino acids. Protein contributes to building components of the body. Protein can also be used to produce energy, since the liver can convert amino acids to glucose.

Fat slows down carbohydrate absorption. Fats essential in the diet are linoleic and linolenic acids.

Fat is converted into fatty acids when digested. Most fats are used for energy or stored for later use (with the help of insulin). When other fuels are in short supply, the level of insulin in the blood falls, and this promotes the removal of fat from storage. This fat goes into circulation and may be used. The metabolism of fat is different to that of glucose. By products are ketones. There are two types of fibre, soluble and insoluble. Soluble helps slow down absorption of sugars. Alcohol is metabolized by the liver, at the rate of approximately 7 to 10 g per hour. In the presence of alcohol, the attention of the liver is taken up processing it, so gluconeogenesis does not take place if needed.

The two hormones insulin and glucagon, both produced in the pancreas, work together to maintain the level of glucose in the blood within the normal range, which is between 80mg/dl and 120mg/dl. (4.4mmol/l - 6.7mmol/l) Insulin production by the pancreas falls into two categories, basal and bolus. The basal production is a constant low level of insulin secretion. The bolus

Food Type	Calorific Content
One teaspoon of sugar	32
One gram Carbohydrate	4
One Gram Protein	4
One gram Fat	9
One Gram Alcohol	7

Table 3.1: Some Energy Contents of Food (Krall & Beaser, 1989)

element occurs after food intake, as the blood glucose level rises, a rapid and large insulin secretion of short duration takes place in response to this rise in blood glucose level.

The hormones from the pituitary, adrenal and thyroid glands have insulin blocking effects.

A balance of glucagon and insulin keeps blood glucose concentration in the normal range.

3.5 Factors Affecting Blood Glucose Concentration

3.5.1 The Effect of Food on Blood Glucose Level

Food is the main factor that increases blood glucose. Three points to be considered about food are Quantity, Type and Timing.

Glycemic Index

Glycemic Index (GI) is a measure for comparing carbohydrate-containing foods on the basis of their effects on post-prandial glucose profiles (Nathan 1987). Studies have shown that Glycemic Index more accurately predicts the blood glucose response to food intake than simple caloric content in IDDM cases (Hermansen et al 1987).

There is data available on the glycemic indices for many types of food. GI data is not used in the current implementation.

3.5.2 The Effect of Insulin on Blood Glucose Level

There are various different types of insulin preparation. The main difference between them is their period of action, they are therefore characterized as short, intermediate or long acting insulins. The period of action of the short acting insulins is around 6 hours, the intermediate from 16 to 20 hours, and the long acting from 24 to 30 hours.

Designer Insulins

Modified protein structure insulins have been developed in order to alter their action profiles. These include both short acting and long acting varieties. The short acting varieties have a more rapid onset and shorter duration than soluble insulins, such as Actrapid. The longer acting ones have more linear action over their period of activity. (Lindholm, 2002)

3.5.3 Exercise

Fuel for muscle comes from glucose and free fatty acids. The glucose comes from the blood and glycogen stored in the muscles and in the liver. Gluconeogenesis converts glycogen into glucose. During exercise, for about the first 15 minutes the energy source is blood glucose and muscle glycogen. After that up to about 30 minutes liver glycogen is used. Amino acids (especially alanine) can be used. After about 30 minutes more of the energy comes from free fatty acids. This reaction does not require insulin and produces ketones. If there is insufficient insulin, the blood glucose cannot be used, so the fatty acids are used. When there is insufficient insulin there is normally a large amount of these in the blood, as well as high glucose levels. The cells inability to use the glucose also stimulates production of more glucose by the liver. Thus exercise in such a state results in raised blood glucose and ketones. Active muscle is more sensitive to insulin than resting muscle, so exercise results in more efficient insulin utilization.

When glycogen stores are used, they have to be built up again. This process takes several hours. Insulin and blood glucose are required for this process. This can lead to hypoglycemia several hours after exercise.

3.5.4 Metabolic Functions Not Requiring Insulin

The brain and central nervous system utilise glucose for their energy requirements, but do not require insulin to do so.

3.5.5 Glucose Excretion by the Kidneys

When blood glucose levels are abnormally high, the kidneys will take action to remove glucose from the blood. Thus glucose will be found in the urine. Checking a urine sample for glucose is a common method of detecting abnormally high blood glucose levels. The level at which urinary excretion of glucose starts to occur is called the Renal Threshold, and this is normally around 160 to 180 mg/dl.

3.5.6 Liver Function

The liver performs conversion between glucose and glycogen. The uptake or release of glucose by the liver is dependent on the levels of glucose and insulin in the blood. At higher levels of both glucose and insulin, gluconeogenisis takes place, and with falling levels the reverse process is performed (Mortimore, 1969). Thus, at low blood glucose levels, insulin will inhibit the action of glucose production. This is what allows patients on insulin to become hypoglycaemic.

3.5.7 The Symogyi Effect

In response to hypoglycaemia, the body takes action to raise the blood glucose level. This is done by the liver converting glycogen to glucose. After an episode of hypoglycaemia, the effect of this action can persist for several hours.

3.5.8 The Dawn Phenomenon

In the early hours of the morning, the body releases a number of hormones, including growth hormone, which release glucose into the blood in preparation for the forthcoming task of rising. In general, these hormones are also insulin blocking. Thus the Dawn Phenomenon is seen as a raise of blood glucose levels in the early morning caused by extra insulin demand due to both the higher levels of insulin blocking hormones and glucose production.

(Krall and Beaser, 1989) (Oakley et al, 1968)

Chapter 4

The Diabetes Control Problem

4.1 Diabetes Complications

Long term living with blood glucose levels above normal values can seriously damage the health of a diabetes patient. High blood glucose levels cause damage to the cell structures that make up the nerves and the blood vessels. Damage to blood vessels and nerves are an unfortunate side effect of long term hyperglycaemia. This damage to blood vessels leads to the common problems of diabetes: blindness, renal failure and infections (especially of the lower limbs) which are difficult to treat because of the damaged circulatory system. Blindness results from diabetic retinopathy, failure of the very small blood vessels of the retina. Similar blood vessel deterioration results in damage to kidney function, which can ultimately lead to kidney failure. Many diabetic deaths are caused by cardiovascular disease, as the blood ves-

sels of the heart become damaged. (Barcelo and Rajpathak, 2001) The nerve damage, once again often affecting the lower limbs, leaves the patient vulnerable to having injury inflicted to themself, and not noticing it, thus leading to further possibility of infection. This can lead to the loss of limbs. Thus, in order to maintain the wellbeing of the patient, the aim of diabetes treatment has to be to keep the blood glucose levels as close to normal as possible.

4.2 Treatment

Type I diabetes is treated by injections of insulin, the doses of which have to be coordinated with the diet to attain a balance between food intake and insulin effect, in order to maintain a blood glucose level within an acceptable range. Blood glucose levels above or below the normal levels are dangerous, thus it is desirable to administer just enough insulin doses so that the glucose levels are kept as close to normal as possible. After the discovery that insulin was the missing hormone which resulted in diabetes, and its isolation from the pancreas by Banting, Best and co-workers, during the period from 1920 to 1922, medical science felt that diabetes had been cured. (http://www.diabetes.ca/) Diabetic patients were given insulin injections, the insulin being that extracted from pig or cattle pancreas. The body was then able to use the glucose, and the constant symptoms of hyperglycaemia and loss of body weight were eliminated.

It was a few years later that it was noted that all was not well with these patients. The symptoms of diabetic complications began to set in.

As well as the long term problems caused by higher than normal blood glucose concentrations, the diabetic on insulin has to be wary of the dangers of the opposite effect, blood glucose falling below acceptable limits as a result of more insulin than is required circulating around the body. Hypoglycaemia, or low blood glucose, results in dizziness, tremors, confusion, sweating, and if not treated soon enough, unconsciousness in the form of a hypoglycaemic coma. The coma results from the brain's requirement for a certain level of glucose in the blood in order to function.

Diabetes is a problem of a lack of insulin and too much glucose in the blood, but the problem with just the opposite arises due to the differences between injecting insulin and having the pancreas produce it naturally. In the second case, the pancreas produces insulin on demand, in response to an intake of food. The duration and quantity of this production will be sufficient to meet the demand. When a fixed dose of insulin has been injected, there is no calling it back, or stopping it from acting. Insulin secreted from the pancreas is sent directly into the bloodstream and has a short duration of action and hence blood glucose lowering effect ends soon after the secretion stops. Conversely, subcutaneously injected insulin takes time to be absorbed into the blood and perform its function. If for some reason there is an insufficient quantity of glucose for it to react with, for example, the patient does not eat enough, takes part in some extra exercise (thus using up extra energy in the form of glucose) or mistakenly injects more insulin than is required, then the injected insulin will cause the blood glucose level to fall below an acceptable level. The patient, or someone else, needs to realise what is happening, and has

to take action in order to raise the blood glucose level. This can be in the form of eating something with sufficient calorific content, or, in cases tending towards coma, an intravenous injection of glucose. The aims of treatment are to restore physiology to as near a normal state as possible, while allowing the patient to live as normal a life as possible. Thus we have a trade-off between these two.

Components of treatment are Insulin, Diet, Education and Exercise.

"Consistency in timing and in food quantities is the best way to achieve good diabetes control. Any compromise can be like shooting at a moving target!" (Krall and Beaser, 1989)

The purpose of this system is to keep track of the moving target so that adjustments can be made to allow for the target to be hit, while dealing with the inconsistencies of living in the real world.

Measuring blood glucose values is the most effective way of knowing if sufficient insulin is available. There is much evidence that better control greatly reduces the risk of complications. Thus increasing the quality of life for the diabetic patient.

4.3 Insulin Therapy

For many years it was assumed that keeping blood glucose levels close to normal would reduce the risk of diabetic complications. This was scientifically

justified in 1993 with the publication of the Diabetes Control and Complications Trial (Diabetes Control and Complications Trial Research Group, 1993). In recent years, the goal of insulin therapy has therefore become to produce insulin action as close to normal as possible, in order to maintain the blood glucose levels as close to normal as possible. Human insulin is available in two different forms: regular, or short acting, which is simply a solution of insulin; and long acting formulations, which are made by adding an excess of zinc ions to the solution, forming an insulin zinc suspension. This increases the duration of action, since the zinc ions encourage the formation of the insulin hexamers. Since it is a suspension, the vial requires suitable agitation before administration in order for the elements to interact.

Blood glucose level control is measured in two main ways: using a blood glucose testing machine to check the current value, and the glycosylated haemoglobin test. Blood glucose level can be checked at any time using a blood glucose testing machine and a drop of blood, usually taken from a finger. A clinical laboratory can take a blood sample and perform a glycosylated haemoglobin test. This gives an idea of the average blood glucose level over a period of three months. This is an important value to monitor, since it is the elevated blood glucose over a period of time that causes the damage to the body that leads to diabetic complications.

4.3.1 Intensive Insulin Therapy

This is a technique which uses either multiple injections or an infusion pump. In the case of multiple injections it takes the form of a single dose of ultra-lente, termed the basal insulin supply, and normally three preprandial (bolus) doses of soluble insulin. Data from self monitoring of blood glucose is used to adjust the treatment.

The aim of the therapy is to mimic the normal physiological action of insulin secretion, in order to maintain the blood glucose level within the required limits. In order to do this multiple injections per day are required, a long acting variety to maintain the basal supply, and short acting doses for the meal related bolus requirement. Insulin doses and food intake need to be coordinated in order to keep the level of glucose in the blood as near to normal as possible. A blood test before each meal is used to determine the amount of insulin to be taken. The philosophy of intensive versus conventional therapy is that daily metabolism, eating and activity are not always the same, and therefore the insulin dose must vary in order to compensate. It is estimated that the normal pancreas constantly secretes about half a unit of insulin per hour, and releases more in response to raised blood glucose levels after the ingestion of food. Thus, the basal/bolus method of insulin doses is emulating this natural insulin release of the pancreas.

4.3.2 Insulin Dose Adjustment

General rule: only make adjustment when abnormal values are noted for three days in a row. Check for other reasons for the abnormal values before deciding to adjust insulin. Only change one dose, and by not more than 2 units at a time.

When rebound could possibly be suspected, reduce the insulin dose that may have caused the reaction precipitating the rebound. This is less dangerous than assuming the opposite and increasing the insulin dose. The hypothesis of rebound can then be checked. Morning hyperglycaemia can be caused by:
(1) insufficient insulin overnight;
(2) dawn phenomenon;
(3) Somogyi phenomenon.

4.4 Exercise

Exercise can be used as part of therapy.

4.5 Education

The more the patient knows, the better they will be able to cope. The diabetic patient must be responsible for his or her own care, they cannot be monitored by a physician 24 hours a day, but they do have to live with

HBA1c Value (%)	Average bgv
5.4 - 7.4	<120
7.4 - 8.5	120 - 150
8.6 - 10.5	150 - 200
10.6 - 13.0	200 - 300
>13.0	>300

Table 4.1: Glycosylated Hemoglobin Levels (Krall & Beaser, 1989)

Before Breakfast	70 -120
Before Lunch, Supper and Bed	70 - 140
1 hr after meal	<180
2 hr after meal	<150
02h00 - 04h00	>70

Table 4.2: Target Blood Glucose Levels (Krall & Beaser, 1989)

diabetes 24 hours a day. This system is an aid to them in taking care of themselves.

4.6 Blood Glucose Metrics

Diabetes mellitus is characterized by above normal blood glucose values. Normal fasting blood glucose values are in the range 60 to 120 mg/dl. After eating it should be not more than 140. The blood glucose value should be back to fasting level three hours after a meal.

(Krall and Beaser, 1989)

4.7 Diet

Diet is an important part of treatment.

Different methods can be used to quantify energy intake. These include diabetic diet exchange lists, counting calories, measuring carbohydrate intake and using glycaemic indices.

There are 4 calories per gram of carbohydrate (CHO) (Beaser and Hill, 1995)

There are 4.185 kilojoules per calorie. (Anderson, 1981)

Chapter 5

The Mathematical Model

5.1 The Model Equation

The mathematical model extrapolates blood glucose value at time t from a blood glucose reading at time 0 using the formula:

$$G(t) = \int_0^t G(0) - I(t) + F(t) - E(t) + H(t) + V(t)dt$$

where

$I(t)$ is the effect of insulin

$F(t)$ is the effect of food

$E(t)$ is the effect of exercise

$H(t)$ is glucose production in the liver

$V(t)$ represents various other factors, both positive and negative, including

the Dawn Effect and excretion of glucose by the kidneys

In order to construct the mathematical model, it was necessary to formulate these functions such that they give the effect on blood glucose level at any given time. Each term in the equation has either a positive of negative effect on blood glucose level. The integral of the representative function over the period of action of an item will produce an area under the curve proportional to its quantitative effect on the blood glucose level.

Thus, the integral of the function representing insulin effect at time t, $I(t)$

$$\int_{t1}^{t2} I(t)dt$$

will produce the area under the curve of the function for the period from time $t1$ to $t2$. It can also be thought of as adding up the effect at all time points over the period.

5.2 Insulin Action Profiles

Insulin action profiles are described in package inserts, and other informational publications from pharmaceutical companies, as well as on pharmaceutical company websites.

A paper by Bottermann et al (1985), gives tables showing time versus concentration and bioactivity, determined using the GCIIS Biostator, for several

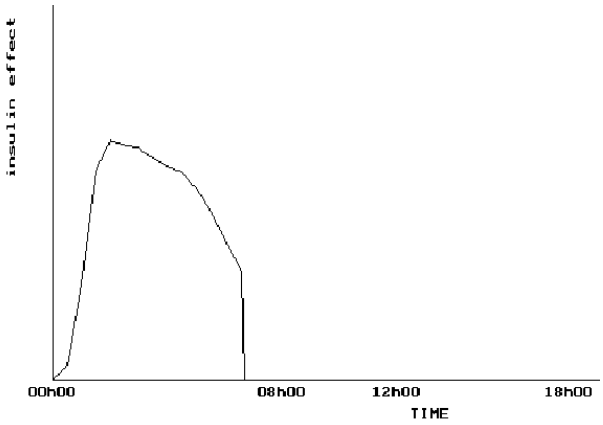


Figure 5.1: Plot of Data for Actrapid from Bottermann et al

different types of insulin.

5.3 Approximation of Insulin Reaction Curves

The initial study was restricted to the two types of Novo insulins Actrapid and Ultratard. Data on the action profiles of these two types of insulin has been published by Bottermann et al (1985). Polynomials could have been used to obtain functions closely fitting the data given in this study, as initially proposed (see Appendix B), however a less complicated approach was taken. Since the effect over a period of time of a few hours is what is important, and not the minute by minute fluctuations of insulin activity, the fitting of a curve more closely approximating the available data is not deemed to be worth the extra costs involved. Furthermore the experimental data at hand can by no means considered to be exact. The use of a sine wave was therefore chosen to approximate both insulin and food reaction curves over their time

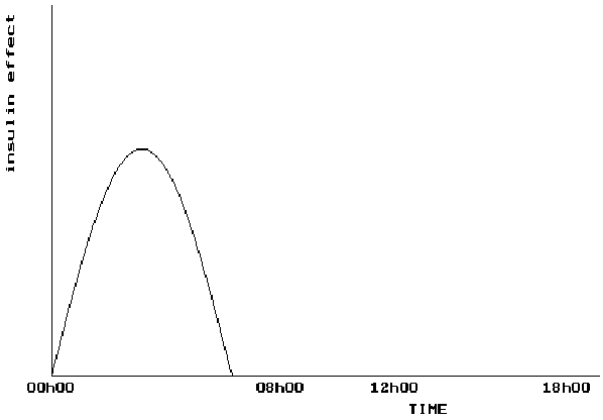


Figure 5.2: Sine Wave

of action. This has been chosen since it is easily generated using the built-in programming language function, and simplifies mathematical manipulation of the function . Such manipulation of the function may need to be done in cases of increased metabolic rate, such as during exercise, which results in more rapid effect of the soluble insulin. Altering the period of action of the sine function is much more simple than performing this manipulation on a polynomial function.

5.3.1 Actrapid

The reaction curve for Actrapid, as explained above, has been approximated by a sine curve.

The equation:

$$a(t) = 1.9635 \sin(\frac{\pi}{8}t)$$

for values of t from 0 to 8 gives a sine curve over the period of 8 hours, having

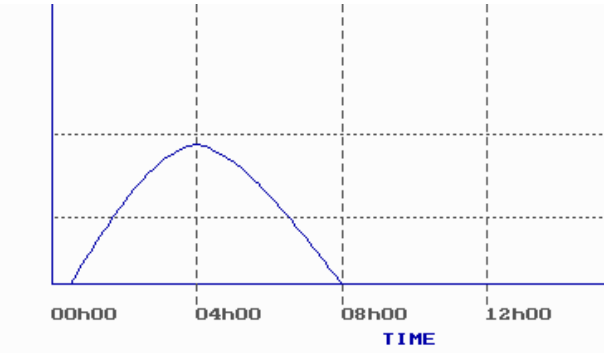


Figure 5.3: Sine Wave Actrapid Function

an integral of value 10.

$$y = \sin(x)$$

for values of x from 0 to π produces one peak of a sine wave (with duration π).

$$y = \sin(\frac{\pi}{8}x)$$

also produces one peak of a sine wave, but the duration is 8 instead of π.
The value 1.9635 is used to adjust the value of the integral of the function over the values concerned (0 to 8 hours) to the desired value. All of the insulin functions have been constructed to have this standard (arbitrary) value of 10 as their area under the curve over their period of action. This forms a basis on which to perform the calculations.
The function for each type of insulin is defined with time values for how long after the injection it starts to work, and how long after the injection the

action terminates. Thus the length of the sine wave peak, or the period of action of the insulin is $I_{end} - I_{start}$.

So, for example, the general form of the sine wave Actrapid equation is:

$$A(t) = A_{peak} * \sin((\frac{\pi}{A_{end} - A_{start}})(t - A_{start}))$$

$$A_{start} \leq t \leq A_{end}$$

Where the constants have been replaced with model parameters.

The term

$$\sqrt{(}\frac{t - A_{start}}{A_{end} - A_{start}})A_{end} - A_{start}$$

varies from 0 to 1 over the period of action of the function, but modifies the progression from linear to non-linear, thus altering the shape of the resultant curve. It is used to skew the action curve to the left, so that the peak effect is closer to the beginning of the period of action, as taking the square root of values between 0 and 1 produces a sequence that starts off increasing quickly and then eases off, producing the value 0.5 one quarter of the way along. This gives a better approximation of the rapid onset of action of Novorapid that a normal sine wave does.

This technique has been used with the functions for Actrapid, Novorapid, Insulatard and Protaphane, as the published action charts for these also show the peak earlier than the middle of their action period. Action charts for Novo

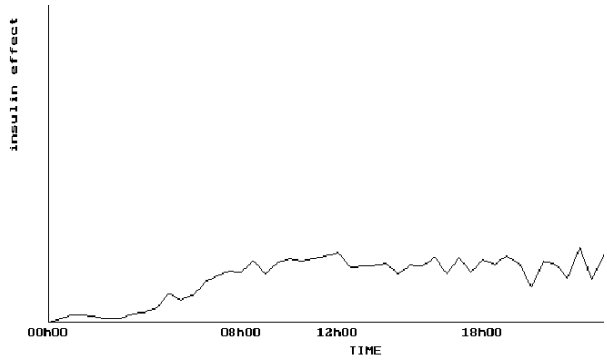


Figure 5.4: Plot of Data for Ultratard from Bottermann et al

insulins can be found on the company website (www.novoproduct.com).

The following equation is being used for Actrapid:

$$A(t) = A_{peak} \sin((\frac{\pi}{A_{end} - A_{start}})\sqrt{(}\frac{t - A_{start}}{A_{end} - A_{start}})(A_{end} - A_{start}))$$

$$A_{start} \leq t \leq A_{end}$$

5.3.2 Ultratard

The action of Ultratard is described by Novo as starting to work after 4hrs, having a peak effect between 8 and 24hrs, and ending after 28hrs.

As a starting point, the function approximating Ultratard was represented by a straight line of action between 8 and 24 hours, with a linear increase from 0 to the 8 to 24 hour level between 4 and 8 hours, and a linear decrease

back to zero between 24 and 28 hours.

The following set of equations give the required function, also having a value of 10 for the integral over the period of action:

$$u = \frac{1}{8}t - \frac{1}{2}$$

for values of t from 4 to 8;

$$u = \frac{1}{2}$$

for values of t from 8 to 24;

$$u = -\frac{1}{8}t + 3.5$$

and for values of t from 24 to 28.

This was subsequently modified to the following sine wave based representation:

$$U(t) = U_{peak} * \sin(\frac{\pi}{U_{end} - U_{start}})(t - U_{start})$$

$$U_{start} \leq t \leq U_{end}$$

based on information from the Novo Nordisk website (http://www.novoproduct.com, 2004).

x	0	0.125	0.25	0.375	0.5	0.625	0.75	0.875	1
$\sqrt{(x)}$	0	0.354	0.5	0.612	0.707	0.79	0.866	0.935	1

Table 5.1: Square Root Function Values

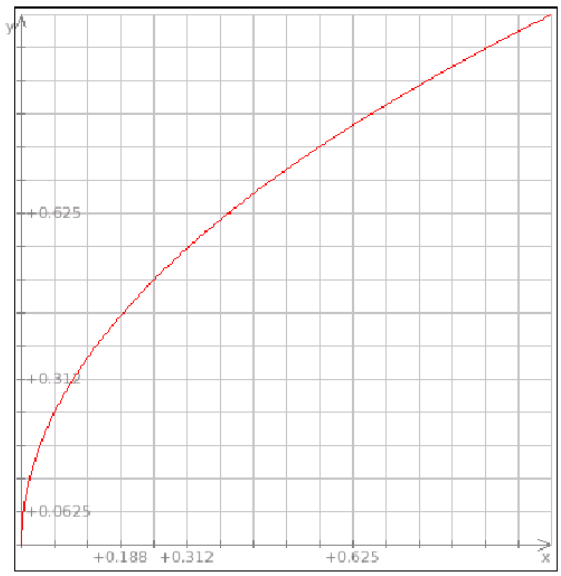


Figure 5.5: Square Root Plot

5.3.3 Novorapid

Novorapid is the insulin aspart preparation from Novo Nordisk. It has a more rapid onset, and shorter duration than Actrapid.

The equation:

$$N(t) = N_{peak} \sin(\frac{\pi}{N_{end} - N_{start}}(t - N_{start}))\sqrt{(}\frac{t}{N_{end} - N_{start}})(N_{end} - N_{start})$$

has been used, based on information from the Novo website (www.novoproduct.com).

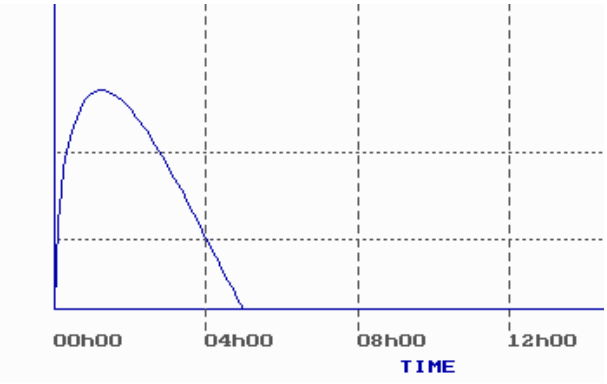


Figure 5.6: Novorapid Function

5.3.4 Insulatard

The action of Insulatard is described by Novo as starting to work after 1.5hrs, and ending after 24hrs.

This is represented by the following sine wave based equation:

$$I(t) = I_{peak} \sin(\frac{\pi}{I_{end} - I_{start}})(t - I_{start})\sqrt{(}\frac{\pi}{I_{end} - I_{start}}(t - I_{start}))$$

$$I_{start} \leq t \leq I_{end}$$

5.3.5 Protaphane

The action of Insulatard is described by Novo as starting to work after 2hrs, and ending after 24hrs.

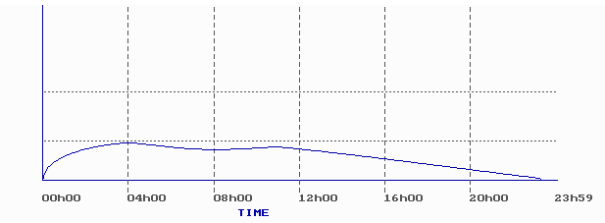


Figure 5.7: NPH (Protaphane and Insulatard) Function

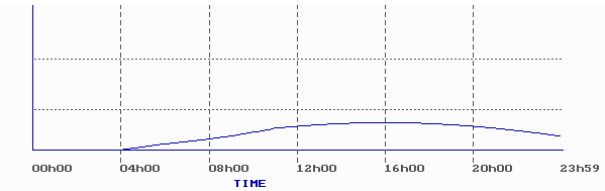


Figure 5.8: Detemir Function

This is represented by the following sine wave based representation:

$$P(t) = P_{peak} \sin[(\frac{\pi}{P_{end} - P_{start}})\sqrt{(}\frac{(t - P_{start})}{P_{end} - P_{start}}(P_{end} - P_{start}))]$$

$$P_{start} \leq t \leq P_{end}$$

5.3.6 Detemir

The Ultratard function has been used to represent the action Detemir. Both are long acting insulins, giving a low level of action over a period in excess of 24 hours.

5.4 The Food Equation

As with insulin types, the different food types have their action determined by model parameters for times of their start and end of action from time of ingestion. Food has been divided into five different types: Sugar, Starch, Protein, Fat and Milk. These food groups are based on the standard diabetic food exchange lists used for diet planning. (Bloom, 1982) (Beaser and Hill, 1995) (Anderson, 1981) This approach has been used as it is fairly simple, most users will be used to this type of calorie counting method, and it gives a reasonably accurate record of food intake. Including a database of foods and their nutritional values (per 100g) was considered as an alternative to this food group method, but was ruled out as adding complexity, and storage overheads, for little extra accuracy in return.

Foods are represented by the sine wave based equation

$$food(t) = amount * food_{peak} \sin(\frac{\pi}{food_{end} - food_{start}}(t - food_{start}))$$

The function

$$\sin(\frac{\pi}{food_{end} - food_{start}}(t - food_{start}))$$

$$food_{start} \leq t \leq food_{end}$$

yields a sine wave of duration $food_{end} - food_{start}$, which is the period of time that the particular food is having its effect, that starts to increase at time $food_{start}$ and returns to value 0 at time $food_{end}$, as desired.
As with the insulin functions, a $food_{peak}$ parameter is used to adjust the value of the area under the curve to fit in with the model.

5.5 The Effect of Exercise on Blood Glucose Level

Physical activity has three major effects on the blood glucose level. The first is the use of the glucose to produce energy required for the activity. The second is an indirect one, since increased activity speeds up the rate at which injected insulin is absorbed into the blood. The third results from the fact that exercise lowers insulin resistance.

In the basic model equation, the exercise effect is another negative term, like the insulin effect. This approach was also used by Salzsieder, Rutscher and Fischer in the KADIS model, where exercise is quantified as insulin equivalents. (Salzsieder, Rutscher and Fischer; 1992)

5.6 Hepatic Glucose Production

In order to represent the action of the liver in blood glucose fluctuation, a function is required which produces an increase in blood glucose levels when

blood glucose and insulin levels are both low. An increase in either one will reduce the value of the function.
The following value is calculated:

$$(G_h - G) - (I - I_h)$$

where

G is blood glucose level
I is insulin level
G_h and I_h are model parameters

If this is positive, then hepatic glucose production is given a proportional value. G_h represents the blood glucose value above which hepatic glucose production does not take place. I_h represents the blood insulin value above which hepatic glucose production does not take place. These two parameters interact, so that both need to be below a certain value before hepatic glucose production will be seen. The table shows function values for G_h with a value of 70, and I_h set to 35.

5.7 Urinary Excretion of Glucose

This is a constant value for blood glucose concentrations over the renal threshold, the model parameter RT represents this value.

G	40	45	50	55	60	65	70	75	80	85
I										
5	90.00	85.00	80.00	75.00	70.00	65.00	60.00	55.00	50.00	45.00
10	80.00	75.00	70.00	65.00	60.00	55.00	50.00	45.00	40.00	35.00
15	70.00	65.00	60.00	55.00	50.00	45.00	40.00	35.00	30.00	25.00
20	60.00	55.00	50.00	45.00	40.00	35.00	30.00	25.00	20.00	15.00
25	50.00	45.00	40.00	35.00	30.00	25.00	20.00	15.00	10.00	5.00
30	40.00	35.00	30.00	25.00	20.00	15.00	10.00	5.00	0.00	0.00
35	30.00	25.00	20.00	15.00	10.00	5.00	0.00	0.00	0.00	0.00
40	20.00	15.00	10.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00
45	10.00	5.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

Table 5.2: Hepatic Function Values, $G_h = 70$ $I_h = 35$

5.8 The Dawn Effect

This has two components. Hormones are released which release glucose into the blood. These hormones also increase insulin resistance in the morning. This is implemented as two functions. The first component increases the blood glucose value during a period in the early morning. DE_{peak} DE_{start} and DE_{end}

The other is the increase in insulin resistance described in the next section.

5.9 Insulin Resistance

This is represented by a sine function having parameters $amIR_{peak}$ $amIR_{start}$ and $amIR_{end}$, lowering the insulin effect during a period in the morning specified by $amIR_{start}$ and $amIR_{end}$.

5.10 The Somogyi Effect

Following a period of hypoglycaemia, a counter regulation causes blood glucose levels to become elevated for a number of hours. The parameters S_{peak}, S_{start} and S_{end} define the elevation of blood glucose during this period.

5.11 Approximations, Simplifications and Model Accuracy

Some factors have not been included in the current model. These include detailed treatment of conversion between glucose and glycogen within the liver, and changes in insulin action during periods of exercise. Data about the Gylcaemic Index of foods has not been included in the food calculations.

The model assumption that the blood glucose lowering effect of the insulin can be based on the pharmacodynamic absorption charts has been backed up by information published by Berger and Rodbard, who state that glucose utilisation appears to be linearly dependent on insulin concentration. (Berger and Rodbard, 1991)

5.12 The Model Parameter Matrix

The model parameters are stored in a matrix. The matrix contains following values:

Peak, Start and End values for the different types of insulin:

1 Actrapid

2 Ultratard

3 Aspart (and Lispro)

4 Insulatard

5 Protaphane

Metabolic model parameters:

0 nirbm

1 ip

2 fp

3 ep

4 hgp

5 de

6 ir

7 rge

8 shr

Peak, Start and End values for the different types of food:

0 Sugar

1 Starch

2 Protein

3 Fruit

4 Fat

5 Milk

6 Beer

7 Wine

8 Alcoholic Spirit

The format of the matrix is as follows:

MPM[i,j,k]	k=1 Peak	k=2 Start	k=3 End
i=1	i_jpeak	i_jstart	i_jend
i=2 j=0	nirbmpeak	nirbmstart	nirbmend
i=2 j=1	ip	0	0
i=2 j=2	fp	0	0
i=2 j=3	ep	0	0
i=2 j=4	hgppeak	hgpg	hgpi
i=2 j=5	depeak	destart	deend
i=2 j=6	amirpeak	amirstart	amirend
i=2 j=7	rgepeak	rgestart	0
i=2 j=8	shrpeak	shrstart	shrend
i=3	f_jpeak	f_jstart	f_jend

5.13 Corrected Blood Glucose Extrapolation

In cases where a subsequent reading has shown the model's predicted result to be inaccurate, a simple linear proportional correction factor has been implemented to adjust the results over the period.

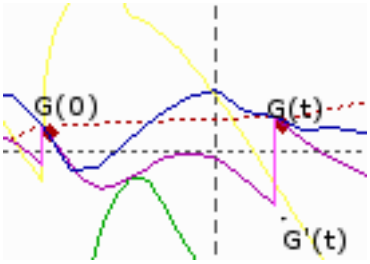
Consider two blood glucose readings, G_0 at t_0 and G_1 at t_1. Let G'_1 be the value predicted by the model by extrapolating from G_0 at t_0. If there is a difference between G_1 and G'_1, then

$$error = G'_1 - G_1$$

the blood glucose value at each time t_x in the period between t_0 and t_1 is adjusted by the correction factor:

$$G'_1 - G_1(\frac{t_x - t_0}{t_1 - t_0})$$

This correction factor subtracts the difference between the line G_0-G'_1 and the line G_0-G_1 from the extrapolated curve to obtain a curve which gives a better approximation of the course of the blood glucose value over the time period of consideration.



This is useful for displaying graphs and analysing averages over day periods to discover trends in blood glucose variation.

Chapter 6

Implementation

The original version of Control Monitor was developed between October 1986 and February 1987. This was implemented using the Pascal programming language and compiled using the NOSC Pascal compiler (from the University of Maryland) on the Sperry Univac 1100/70 mainframe computer of the Natal Technikon Computer Centre. The program was then converted in April 1987 for use on an IBM-compatible Personal Computer (PC) system running MS-DOS. This was done using the MicroSoft Pascal compiler. In May 1992 the program was modified to use the TurboPascal compiler from Borland, in order to add graphical output routines. In 2003, the program was updated and compiled using the FreePascal compiler allowing it to be run on OS/2, FreeBSD, Linux and Windows platforms.

6.1 Source Code Structure

The program consists of a main program component, and a number of supporting modular units. The code is divided into the following components:

6.1.1 Control.pas

The main program file.

6.1.2 Utilmod.pas

A set of general utility routines.

6.1.3 Menu.pas

Implements the user interface.

6.1.4 DataUnit.pas

Defines data structures and handles data files.

The Data Record

The data is stored in the system in the form of a variant record, defined as follows:

```
Data=Record
              Link:Pointer;
              Date:DoubleInt;
              Active:Boolean; {false if record deleted or disregarded}
              DType:DTypes;
              Case DTypes of
              ADose:(dtime,cutoff:Integer;  {min from midnight}
                     Units:Integer;
                     itype:itypes);
              GlucVal:(gtime:Integer;  val:Integer);
              Weight:(mass:Integer); {Kg}
              Food:(ftime:Integer; ftype:Integer; amount:Real);
              Hba1:(hval:Real); {Glycosolated Haemoglobin}
              BP:(bptime,systolic,diastolic,pulserate:Integer); {blood pressure}
              Exercise:(level:Integer;        {physical exertion}
                        time1,time2:Integer)  {start and stop times}
            End;

MPM:Array[1..10,0..7,1..3] of Real;
{Model Parameter Matrix}
{1..10 elements used by model}
{items within the elements - up to 8 of them}
{peak, start and end values for the items}
{1 insulin}
{actrapid, ultratard, novorapid}
```

```
{2 basal metabolism}
{3 food}
{4 exercise}
{5 liver function}
{6 dawn effect}
{7 morning insulin resistance}
{8 kidney function}
{9 hypoglycaemic rebound}
{10 insulin,food,exercise multiplier parameters}
```

6.1.5 Insulin.pas

Provides functions to approximate insulin reaction curves.

6.1.6 Foods.pas

Provides functions to approximate effects on blood glucose of different types of foods.

6.1.7 Model.pas

Implmentation of the blood glucose prediction model.

6.1.8 Graphix.pas

Procedures for drawing graphs.

6.1.9 TxtPlot.pas

Provides graph drawing routines for text screens.

6.2 The Model Parameter Matrix

The model parameters for insulin and food functions are stored in a multi-dimensional matrix, the Model Parameter Matrix, a multidimensional array. Most entries consist of the three values per item: peak magnitude, start time, and end time.

The final line with first value 9, stores blood glucose units, mg/dl (default) or mmol/litre, and whether to calculate and display the average blood glucose value for the day. The default is to have this setting off. Values of 0 indicate the default and 9 for non default are used.

Chapter 7

Functions of The Control Monitor System

As described in Chapter 1, the primary function of the system was to implement the mathematical model. This includes a database element to store the data items related to blood glucose changes.

The system also has the facility to store some other clinically useful data. Diabetics are encouraged to keep records of at least blood glucose readings, in addition records of insulin doses and food intake are useful. The data required by the system for blood glucose extrapolation forms the base of a detailed record system. In addition to these values, the system also allows the entering of body mass, blood pressure readings (systolic, diastolic and pulse rate) and glycosylated haemoglobin values.

7.1 Running the System

To set the program up to run, copy the executable program file called *control* on Unix systems, or *control.exe* for DOS, Windows and OS2 systems, into a directory (or folder) where the program and associated data is to be kept. The file mpmatrix which contains the model parameters also needs to be copied into the same directory. Finally, a subdirectory called data must be created within the one where the executable is located. Type *control* at the command prompt to start the program. The menu Screen will appear.

7.2 Menu Options

The screen provides a list of choices numbered 0 to 16.

0 Terminate

Exit the system. If model parameter values have been edited during the session, the program will ask if the changed values should be saved. Press y to save the changed values, or n to leave the stored values unchanged.

1 Enter Insulin Dose Data

Time, size and type of insulin are required. Times are in 24 hour clock format, HHMM. The default value in the time field is the current time.

2 Enter Blood Glucose Data

Blood glucose readings can be entered in mg per dl or mmol per litre. Entering the special value of -33 records a hypoglycaemic event. Time and blood glucose concentration are required.

3 Enter Food Data

For each item of food to be recorded, the time. quantity and type are required. The default value in the time field is the current time for the first item entered, and is the value entered for the previous item when a list of items are entered. This speeds up data entry when entering a meal consisting of a number of different types of food, as the time value will be the same for all of them. The default quantity is 1.0.

4 Enter Exercise Data

To record a period of exercise, start time, end time, and exercise level are required. A level of 1 corresponds to walking, 2 to cycling.

5 Enter Mass Data

Body mass in Kg can be recorded for a particular date.

6 Change Model Parameters

Model parameters and system settings can be altered. Follow the prompts to change the values.

7 Increment Date

Change the date to the day after the current one

8 Change Date

Choose another day. Enter a date in the format YYYYMMDD. The default value is the previous day.

9 Blood Pressure Reading

Time of reading, diastolic and systolic values, and heart rate are required.

10 Display Data for Day

Produces a list of data records held on the system for current day.

11 Edit Data

The list of data for the current day is presented. Use the arrow keys to move up and down the list. Values in records can be changed, and records can be

deleted. Press ENTER on the highlighted record to edit it. Press DEL on the highlighted record to remove it from the system.

12 Plot Graph

A graphical display of blood glucose variation over the day is displayed, together with the effects of food and insulin. A scatter plot of blood glucose readings between two dates can also be produced.

13 Prepare Report

A report including blood glucose reading averages and variation, is produced. Enter a start date and an end date for the period of the report.

14 Extrapolate bgv

A predicted value of blood glucose level at a chosen time of day is displayed. Enter the desired time for the predicted reading.

15 Text File Input/Output

Data records between two selected dates are written to a text file. This feature allows data to be transferred between versions of the program running on different types of computer system. Data file formats are specific to particular compilers and operating systems, but plain text files are compatible

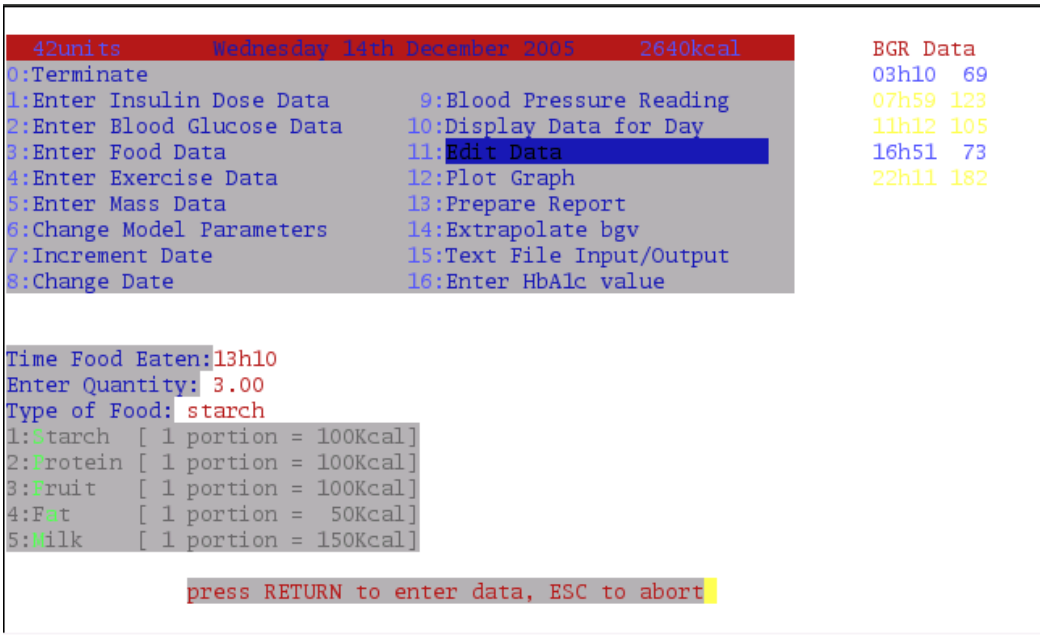


Figure 7.1: Data Input Screen

across various systems. A file name, start date and end date are required. The default file name is data.txt.

16 Enter HbA1c value

The HbA1c value for the current date is stored.

7.3 Producing Reports

The data held by the system can be used to produce reports. These reports are useful at clinics, since they provide a clear record of blood glucose readings, insulin doses, and other useful clinical data. The report summary

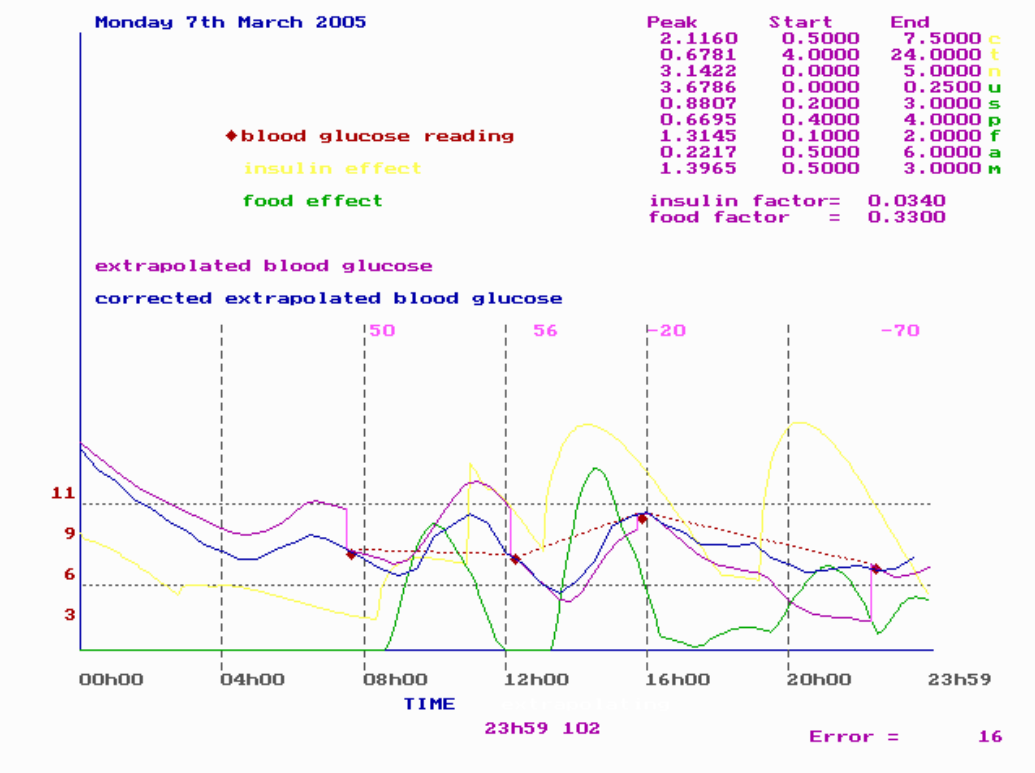


Figure 7.2: Graph Screen

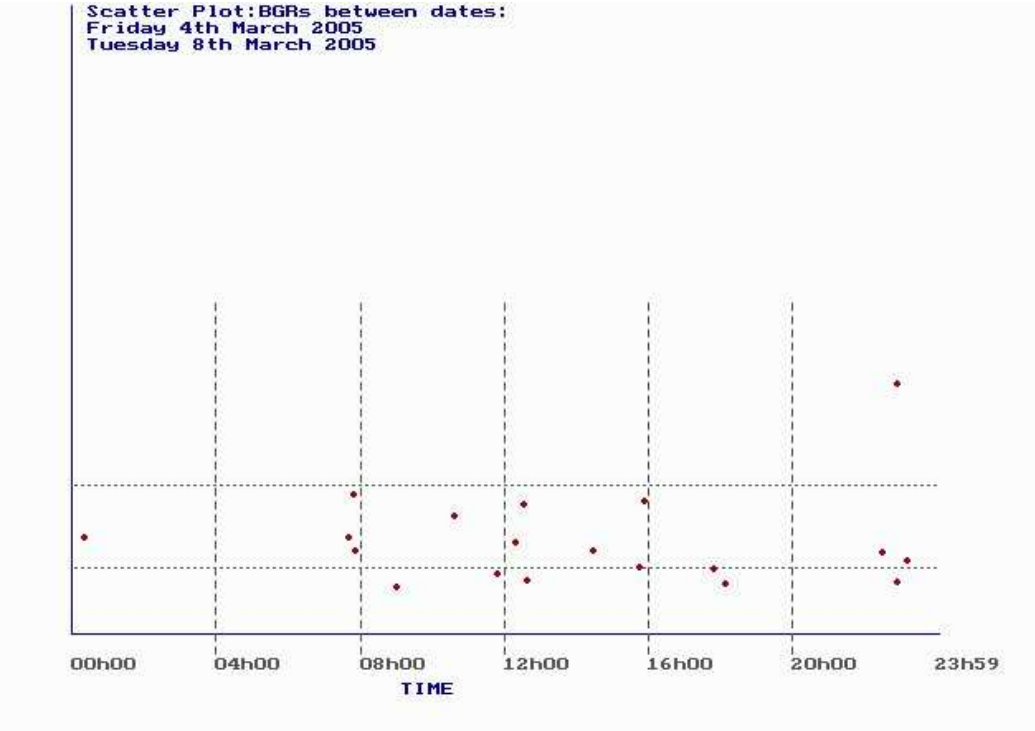


Figure 7.3: Scatter Plot

shows average blood glucose reading values and standard deviation for all readings within the selected date range, as well as these values for a number of subperiods of the day.

A scatter plot of blood glucose readings versus time of day is one of the available graphics outputs. This is a useful tool in looking for trends in blood glucose variation.

The usefulness of this type of reporting and analysis is highlighted in a study by Strowig and Raskin (1998) where they compared blood glucose control within a set of 22 patients over a period of 24 months. The patients were under intensive treatment, with frequent contact with their health care team, and so therapy adjustments could be made frequently if required. During the first 12 months the subjects were using a standard blood glucose meter and recording their results in a logbook, and during the following 12 months they were using a blood glucose meter which stored the results in memory, and the results were then downloaded to a computer for analysis.

The result was an improvement of 10% in HbA1c values, with the overall average decreasing from 7.0 to 6.3, which is noted to be a clinically meaningful reduction in risks for long term complications. This positive result was attributed to the computer generated analyses making the test results more meaningful, easier to organise and evaluate, and enhancing the ability for the patient to discuss the results with their health care professionals.

The computer output displayed the results as statistical summaries showing average number of tests per day, percentages of readings below, within and

above range, average and standard deviation for time periods of the day, plots of all readings against time of day showing times at which readings were within range, and a bar graph of number of readings over six ranges of blood glucose value. This is a similar set of summaries to those produced by Control Monitor. Strowig and Raskin (1998) note that the findings of the Diabetes Control and Complications Trial (DCCT, 1993) equated a lowering of HbA1c results by 10% equated to a 43% decrease in the risk of progression of retinopathy.

Chapter 8

Results

8.1 Measures of Performance of the System

The accuracy of the model, and hence the usefulness of the system, can be accessed at two levels: long term and short term.

The short term accuracy is decided by the difference between actual and predicted blood glucose values.

The most widely used method for assessing the long term level of control is the glycosylated haemoglobin test. The longer term effectiveness of the system is ascertained by reduction of glycosylated haemoglobin value through the use of the system.

8.2 Blood Glucose Value Extrapolation

The model input data that is the most difficult to quantify accurately is food intake. Thus, this has the greatest impact on the accuracy of the predictions. In the output below uses 3 measures of error: [1] the actual difference between predicted value and a reading at the time of the reading, [2] if the actual and predicted values fall in the same range (too low, alright, too high), and [3] the sum of all errors for the day.

1. In the original proposal for the system (Appendix B), it was noted that if predictions could be within a figure of around 25 mg/dl of the actual blood glucose value, then the system would be good enough to be useful. From the figures below, it can be seen that the error is often way above that.

2. The readings have been put into the three categories of below acceptable, good enough, and too high. In the output below, the symbols "-" to show too low, "*" for in range, and "+" for too high. The two symbols at the end of the line show the range of the actual and predicted values. If they are both the same, then the prediction is counted as being a "good prediction", where the actual and predicted values are both in the same category. The final lines show the numbers for where they match, or the predicted value is in a range above or below the real value. In the example data used here, they matched in 17 out of 22 cases. (Unfortunately, in this data set, the only recorded incidence of hypoglycaemia was missed, 21:16 on 1st May, where the model predicted an in range value.)

3. The "Total Error for Day" just adds up the errors. If there are a few readings in the day, and if there are inaccuracies in absorption timings in the functions, then the actual rate of change of blood glucose level will be different than that shown by the model. If there are differences along the way, but they both get to a similar value in the end, then the errors will cancel each other out.

Example Set of Data: Values for May 2007:

```
20070501
07h25: Actual Value:212  Predicted Value: 307  Error:  95  ++
12h49: Actual Value:109  Predicted Value:  88  Error:  -21  **
21h16: Actual Value: 58  Predicted Value: 189  Error:  131  -*
Total Error for Day=  205

20070502
11h20: Actual Value:214  Predicted Value: 205  Error:  -9  ++
17h05: Actual Value:175  Predicted Value: 124  Error:  -51  **
22h22: Actual Value:311  Predicted Value: 214  Error:  -97  ++
Total Error for Day= -157

20070503
11h00: Actual Value:255  Predicted Value: 250  Error:  -5  ++
17h05: Actual Value:177  Predicted Value: 126  Error:  -51  **
22h03: Actual Value:236  Predicted Value: 231  Error:  -5  ++
```

```
Total Error for Day=  -61

20070504
07h33: Actual Value:229  Predicted Value: 259  Error:  30  ++
11h23: Actual Value:148  Predicted Value: 164  Error:  16  **
22h58: Actual Value:220  Predicted Value: 195  Error:  -25  +*
Total Error for Day=   21

20070505
11h05: Actual Value:162  Predicted Value: 159  Error:  -3  **
14h27: Actual Value:135  Predicted Value: 127  Error:  -8  **
21h13: Actual Value:257  Predicted Value: 227  Error:  -30  ++
Total Error for Day=  -41

20070506
08h24: Actual Value:319  Predicted Value: 233  Error:  -86  ++
13h24: Actual Value:295  Predicted Value: 176  Error:  -119  +*
18h27: Actual Value: 77  Predicted Value: 226  Error:  149  *+
21h45: Actual Value: 77  Predicted Value: 164  Error:  87  **
Total Error for Day=   31

20070507
12h02: Actual Value:212  Predicted Value:  95  Error:  -117  +*
21h40: Actual Value:266  Predicted Value: 279  Error:  13  ++
Total Error for Day= -104
```

```
20070508
07h36: Actual Value:220  Predicted Value: 273  Error:  53  ++
Total Error for Day=   53

Below:3
Same level:17
Above:2
```

8.3 HbA1c

The analysis here correlates HbA1c results with two different measures of average blood glucose levels. The average blood glucose value over the period of three months before an HbA1c test was calculated both as the mean of the test results recorded over the period, and as the mean of the average value of a blood glucose function for each day, constructed using a mathematical model.

The average value of a function f(x) between x = a and x = b is defined as:

$$Av = \frac{1}{b-a}\int_a^b f(t)dt$$

(Goodman, 1980)

Table 8.1: Blood Glucose Averages and HbA1c Results

AvBGV	HBA1c	CalcAv
10.9	8	10.4
11.5	8	9.4
9.6	7.9	7.9
9.2	7.7	7.7
9.9	8.7	9.3
8.8	7.6	8.5
9.2	7.4	8.0
9	7.6	7.9
9.9	8.2	8.7
9.2	8.4	8.1
8.4	7.2	7.9
9.5	8.4	8.9
9.9	8.1	8.4
9.8	8	9.2
10.3	8.3	9.2

The blood glucose function is calculated from the mathematical model's extrapolated value, with a correction applied for each interval between two test results where the extrapolated value differs from the test result.

Averages using both methods were calculated from a set of data over a period which included 15 HbA1c tests.

The values calculated using the average value of the model's calculated blood glucose function are seen to give a closer correlation with the HbA1c test results. One explanation for this is that the mean of the set of recorded blood glucose tests will often give a value on the high side, due to the fact that blood glucose sampling will tend to be done more often when values are running high. In the event of hypoglycaemic symptoms, the action taken will be to eat, rather than perform a blood test. Conversely, in the case

of hyperglycaemic symptoms, the blood glucose level is likely to be checked before an extra dose of insulin is taken. A number of tests may then be performed, while the values are still high, while attempts are made to retaurn the value to an acceptble level.

8.4 Discussion

The system provides information to aid monitoring and management. No trial of the system against a control situation has been conducted.

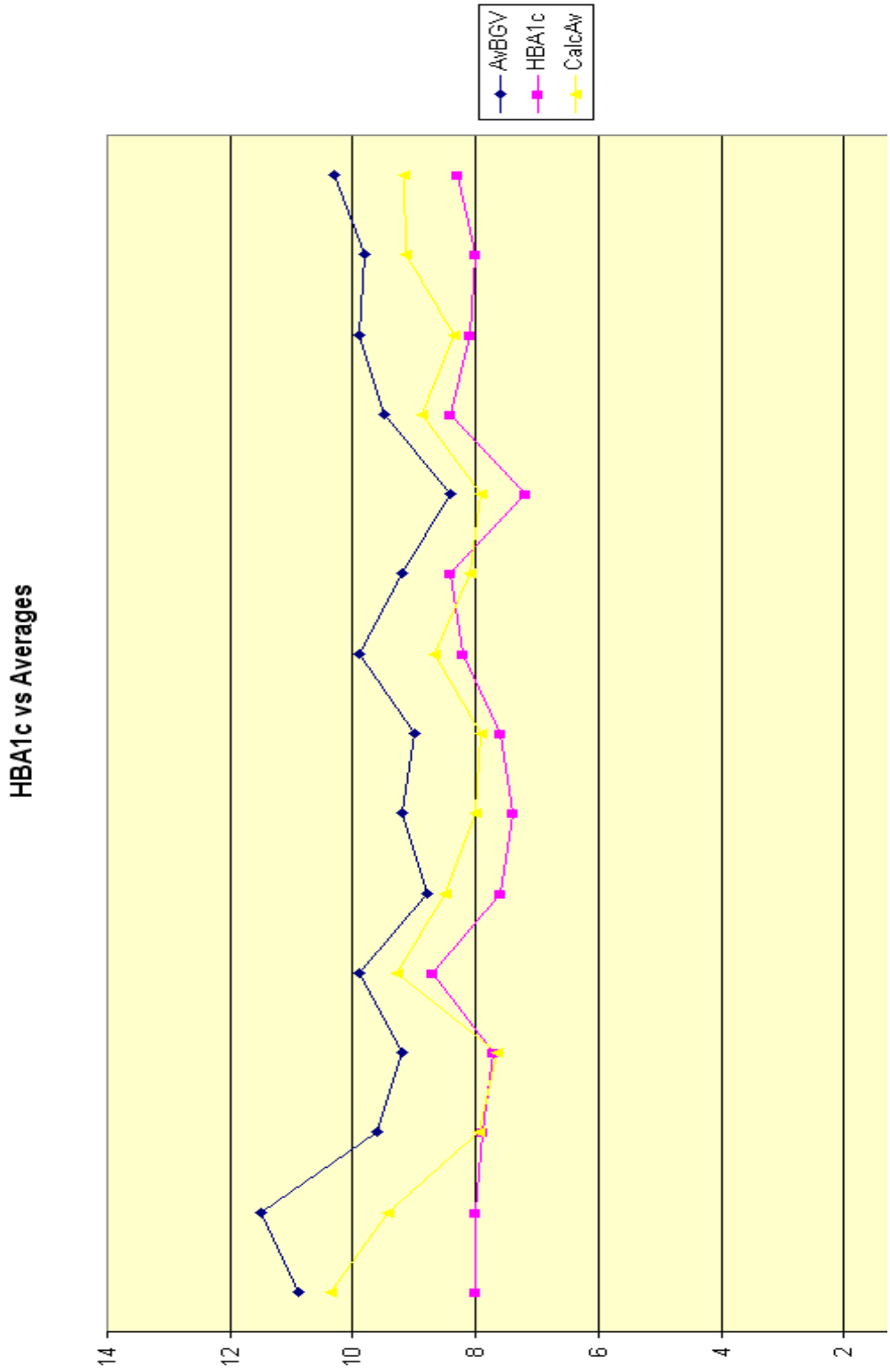


Figure 8.1: Avg BGV, Calculated Avg and HbA1c

Chapter 9

Some Other Diabetes Related Systems and their Impact on Diabetes Care

This chapter looks at some of the other systems that have been developed to assist with diabetes care. Consideration is given to how these systems have made positive contributions to diabetes care. Some comparisons to Control Monitor are made.

Motivation for the development of computer systems systems to assist in the treatment of diabetes has been that the expertise required to treat diabetes is lacking in most sectors of the health service. (Deutsch et al, 1989)

9.1 Origin of Ideas and Groundwork in this Field: 1981 - 1990

9.1.1 Home Blood Glucose Monitors

The first of these were available in the late 1970s. Without this technology, none of this type of system could exist.

9.1.2 Skylers Algorithms

Skyler and Skyler developed a set of insulin dose adjustment rules based on SMBG values. (Skyler et al, 1981) Using four blood test results at fixed times of the day, they suggest insulin dose adjustments. A number of systems that have been developed to provide dose adjustment advice have used these.

9.1.3 BCMC

A study by Schiffrin et al (1985), showed significant improvements in control resulted through the use of a computerised dose adjustment system. This system was implemented on a Hewlett Packard 41C advanced programmable pocket calculator. The patients were required to enter 4 blood glucose readings per day, and the system produced recommendations concerning dosage adjustment and relative time between the insulin injection and the meal based on Skylers Algorithms.

The system was tested on a group of seven patients over a period of 8 weeks. During the trial period, the group mean HbA1c value was reduced from 11.7 to 9.6, and there was a reduction in the average value of the pre-meal blood glucose values.

It was noted that in a situation where a patient did not follow a regular diet pattern or where the diet was inconsistently constituted, this would have an undesirable effect on the success of the system. Therefore, changes in caloric intake and exercise would also need to be taken into account to make the system more usable in real world situations. Due to memory limitations the system could not cater for other special situations, such as illness. This was the first successful computer based system applied to diabetes control (Hovorka et al,1990). Unlike Control Monitor, it did not use a mathematical model, the calculations being based on Skylers Algorithms.

9.1.4 Early Publications on the Subject of Model Based Systems

Worthington (1990) describes the glucose control problem as a classic control system requiring a model of the system being controlled, having predictive capability, and a strategy which is used to control the system using the model as a guide. The advantages of a continuous-time model over a discrete-time model are described. In the case of a discrete-time model predictions are only made with respect to fixed times and adjustments to therapy can only be made at the fixed times. The discrete-time models are the most

common type, and also the simpler and less powerful. The observation is made that the area in which information is most lacking is in quantitative models concerning food transformation into glucose in the blood. The use of the glycemic index is cited as the best available approach. An open-loop control system based on a parametric continuous-time physiological model, which leaves therapy adjustment decisions up to the patient, is recommended as the most attractive approach.

Worthington is describing a system like Control Monitor as being the best type of system for the task.

9.2 Early Systems: 1985 - 1999

9.2.1 Pernick and Rodbard's Monitoring and Dosage Adjustment System

This is a flexible system with many features, not all of which have to be used to make the system useful. It is able to keep track of blood glucose readings, insulin doses, hypoglycaemic events, urinary ketones, diet, activity, weight, illness, and comments to explain out of range blood glucose values. Food intake is quantified relatively rather than absolutely. A meal or snack is assigned a value between 0 and 5, with 3 indicating the usual amount, and a lower value showing less was eaten or a higher value indicating more than normal was eaten.

9.2.2 AIDA

AIDA - the Automated Insulin Dosage Advisor. The first version of AIDA was constructed by adding a KBS to the mathematical model developed by Boroujerdi and co-workers in 1987 (Lehmann and Deutsch, 1996). The system (KBS) used the simulator to examine proposed changes to diet and insulin therapy on blood glucose control. Version 2 (MK II) used an enhanced model, and a KBS with a larger number of time periods in the day. The periods were flexible, whereas the ones in the first one were fixed and tied to meal times.

The motivation behind the development of this system was that while diabetes management is a data rich subject area, little use of the available data is used in typical diabetes situations. (Lehmann and Deutsch, 1996) This has been one of the most successful systems in terms of number of users and number of years in use.

9.2.3 DIAS

Described as the first model based used in clinical practice. (Cavan et al, 1996) The system uses a mathematical model to fill in the gaps between blood glucose readings by providing hourly estimates of blood glucose value. DIAS is noted as being the first clinical application of a computer system documented in the literature, to diagnose previously undetected overnight hypoglycaemia in a patient. (Cavan et al, 1998)

9.2.4 DIABLOG

Biermann and Mehnert (1990) have developed a system called DIABLOG. This is a program designed to teach patients about insulin therapy, since in order for the patient to adjust insulin effectively, a good understanding of glucose/insulin dynamics is required. It is intended to work in conjunction with normal diabetes education and insulin adjustment algorithm programs. The program allows the patient to see graphical extrapolation of blood glucose value from input of food and insulin. The program was developed for use without supervision.

Unlike others, this program is not intended to shift the decisions for therapy changes from the patient to the computer, but to teach he patient about glucose/insulin interactions.

The program uses a mathematical model to simulate the blood glucose profile for an example patient, given a set of food and insulin inputs.

Responses obtained by patients who tested the system were as follows: One third of the patients were confused since the 'computer patient' responded differently to the way that they did. To overcome this problem the model will have to be adjusted for individuals. Most patients found it helpful, ones who did not were those of long standing diabetes feeling that they knew all the program had to teach, and those who had difficulty understanding the meaning of the output.

9.2.5 Prototypical Systems - Ideas and Concepts

As well as those systems implemented and applied, a number of prototypes were described, including a qualitative algebra logic based system (Deutsch et al, 1989), one based on an adaptive control model (Hovorka et al, 1990), and DIABETEX, a knowledge based system, which collects data about the patient, and then calculates a proposal for insulin dosing (Zahlmann,1990). The logic system uses a logical model based on qualitative algebra to define a relationship between glycemic response and changes in insulin dose, site and time. The effects of diet and life-style are assumed to be constant Diet and activity are also assumed to be constant in the adaptive control model system.

9.3 Recent Systems: 2000 onwards

9.3.1 HumaLink

Humalink was originally developed as a patient support and advice system that patients interacted with over the telephone. It is now an Internet based client-server telemedicine system.

In a controlled trial using 22 patients, all experiencing frequent episodes of hypoglycaemia, HumaLink was shown to be a useful tool for reducing the number of hypoglycaemic episodes. During a two month period, the 22 patients entered their blood glucose reading, insulin dose, food and lifestyle data

into the system. The estimated time for this activity was 10 minutes per day. For half of the patients, their care providers were shown the blood glucose predictions generated by the system. For the other 11, the care providers were only given the data that the patients had entered. In both cases, the care providers used the information to make adjustments to therapy. In the group where the predictions were displayed, the incidence of hypoglycaemic episodes was reduced from an average of 1.8 times per week to 0.2 times per week. There was no significant change in the control group, the weekly average figures being 1.8 at the start and 2.0 during the trial period. Total average daily insulin intake remained unchanged for the control group, while it decreased by an average of 9 units per day for the prediction group. Average pre-meal blood glucose reading and HbA1c values both remained unchanged for both groups.

The study concluded that blood glucose prediction can be used to reduce the frequency of hypoglycaemic episodes. (Albisser et al, 2007)

9.3.2 Librae Body Double

Librae Body Double was developed at Robert Gordon University in 2005 with the intention of selling it as a tool to assist with diabetes control (Franklin et al, 2005). This is another mathematical model based system with very similar objectives to Control Monitor. As with Control Monitor, it was designed to be used by the IDDM patient to enter data about blood glucose level, insulin and food to produce blood glucose predictions. Developed 19

years after Control Monitor, it was described as groundbreaking research in 2005 on connecttothenet.com. As with Control Monitor, Librae can produce colour coded output of blood glucose predictions to highlight whether values are in or out of range. Some results are given in Franklin et al (2005). Data was collected from 18 subjects. For the published data analysis, only the data from 11 subjects where the most accurate predictions had been obtained was used in the statistical analysis of performance of the system. It is therefore not possible to get an overall idea of the accuracy of the system, as a large proportion of the data was discarded and not included in the accuracy statistics. The published results give a mean error of 0.35 and standard deviation of 5.99. With this carefully selected subset of the data, 50% of the predicted values were in the limits of -2.44 to +3.6 mmol per litre of the actual values.

A company was set up to sell Librae as a commercial product. The project was abandoned and the company closed down after the attempts to market it failed. (http://www.companieshouse.gov.uk)

9.4 Benefits of using the Systems

It has been observed that blood glucose self-monitoring decreases over a few months after initial diagnosis due to the fact that patients feel that little attention is given to blood glucose logs that they present at clinic visits. (Peel et al, 2007) Many patients present false blood glucose test values to health care professionals at consultations. Actual test values are altered to

make them look better, and extra ones are added to make it seem that they test more often than they do. The data analysis, interpretation and display function of computer systems (such as Control Monitor) can help to motivate patients to frequently perform their blood glucose tests and accurately record the results. (Pernick and Rodbard, 1986)(Strowig and Raskin, 1998) In a literature review of published controlled, randomised trials on the use of emerging technology interventions to enhance diabetes care, Jackson et al (2006), reported that for the studies that they considered, significant improvement in HbA1c values resulted in 6 out of 14 interventions where the subjects had Type 2 diabetes, and 12 out of 15 where the subjects had Type 1 diabetes.

9.5 Problems, Issues and Limitations

Pernick and Rodbard (1986) described getting the data into the system as a major problem. Some of the overheads in this respect have been reduced with the development of blood glucose monitors which store test results, and can be connected to a computer to download the stored data. (Strowig and Raskin, 1998)

Most of the systems limit the adjustment to insulin doses, and assume diet to be constant.

9.6 Comparison of the Systems

9.6.1 Historical Perspective and Originality of Concepts

According to Albisser et al (2005), the concept of computer based glucose prediction was first suggested by Deutsch, Boroujerdi, Carson, Harvey, Sonkson, Tamas and Williams in 1989. However, Pernick and Rodbard, in the description of the system that they developed, suggest that it could be improved by basing it on a pharmacokinetic model instead of rules using Skylers Algorithms. In the same document, Pernick and Rodbard describe the use of computers to assist with the management of diabetes to be in an early and experimental stage. (Pernick and Rodbard, 1986) Thus, references in the scientific literature suggesting the value of developing such a system of the type described in this document, and hence implying that such a system had not been developed, were appearing some years after 1986, when this system was designed. This system was therefore one of the first of its kind.

The majority of the systems described in the scientific literature assume food intake to be constant, and at fixed times of the day. One of the aims of Control Monitor was to allow dynamic control of blood glucose levels by taking into account variations in food intake, and being able to record and quantify their effects on blood glucose level fluctuation.

9.6.2 System Viability and Survival Periods

A downfall of Librae was the complexity of the method used to enter information about food intake. Control Monitor has avoided this problem by using a more conventional method of food exchange lists, familiar to most people with diabetes. Other systems have also followed this approach.

The DIAS system is no longer being developed or maintained. It was only ever used in a small number of trails to produce results for publication, and never saw any real world practical application.

While originally intended as a dose adjustment system AIDA, the Advanced Insulin Dose Advisor, has never been used as such. The implementors decided that it was not accurate for that, and released it as an educational toy. It is still available for download and is therefore one of the longest surviving such systems.

HumaLink is still an active project. Control Monitor has been in operation and use for over 22 years.

9.6.3 Range of Platforms Supported

AIDA does not run on the current version of Windows - Vista. It terminates with an error message about 16 bit DOS applications not being supported in the mode required.

HumaLink runs on Windows XP and will not run on any of the earlier ver-

sions of Windows. It has been implemented in Microsoft Visual Basic. The main problem being the access control functions embedded in the application to interface with the security features within Windows. These Application Program Interfaces (APIs) have not been consistent across different versions of Windows. It has been reported that with some configuration changes, HumaLink can be run on Windows Vista (Albisser AM, personal communication, June 2009).

Control Monitor, as a result of the fact that it has been implemented in standard Pascal, and therefore can be complied with both FreePascal and GNU Pascal, is able to be used on a very wide range of systems. It has been executed on computer systems running the operating systems Sperry-Univac Exec VIII, MS-DOS, IBM OS/2, Linux, FreeBSD, OpenBSD, Windows 3.1, Windows NT, Windows 95, Windows 98, Windows 2000, Windows XP and Windows Vista, and has the potential to be implemented across the vast range of platforms supported by FreePascal and GNU Pascal. This includes Solaris, all of the BSD family of operating systems, most if not all types of Unix, and all versions of Windows. (www.freepascal.org, www.gnupascal.org)

Chapter 10

Conclusions

The number of publications, systems developed, and resources expended in this area show that IT is useful as a tool to aid the treatment of diabetes.

The overheads in terms of data collection of the mathematical model approach are high, and limit the intensive use of this method. A large amount of data has to be collected and entered into the system, and it has to be accurate and complete for the system to be able to function as intended. Thus, it may not be suitable for all people, or for use all of the time by those who do choose to use it. It can be a very useful tool in the right situation.

Published evidence strongly suggests that Control Monitor was one of the first comprehensive data management systems for diabetes, and one of the first computerised systems to use a predictive mathematical model as a practical tool for optimising insulin therapy and blood glucose control.

The system developed here has proved to be a useful aid as a decision support system for dosage and diet adjustment, thus confirming the original hypothesis of the document outlining the motivation for development of the system (see Appendix B).

Storing and analysing data relevant to diabetes control aids overall treatment. Having self-monitored blood glucose values in an ordered and meaningful format at clinic visits greatly aids the process of evaluating and adjusting therapy. The patient is motivated to perform these tests accurately and frequently when it can be seen that the test results are being put to good use. Such contributions help to maintain the health of the diabetic patient.

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The developers of the FreePascal compiler. They have enabled an old program to run on modern systems.

Appendix A

Example Report Output

```
Data Report for Michael Hill

Sunday 1st June 2003
 Food intake: 1.0 of Protein at 00h10
 Food intake: 0.5 of Fruit at 00h10
07h49:Glucose value of   63mg/dl recorded (3.5 mmol/l)
 Food intake: 1.0 of Fruit at 07h55
 Food intake: 0.3 of Milk at 07h55
08h10: 10 units of Ultratard taken
10h55:  8 units of Novorapid taken
 Food intake: 1.5 of Starch at 11h00
 Food intake: 1.0 of Milk at 11h00
 Food intake: 0.3 of Fruit at 11h00
13h15:  8 units of Novorapid taken
13h16:Glucose value of  158mg/dl recorded (8.8 mmol/l)
 Food intake: 3.0 of Starch at 13h30
 Food intake: 1.0 of Fat at 13h30
 Food intake: 0.5 of Protein at 13h30
 Food intake: 1.0 of Fruit at 13h30
19h05:  8 units of Novorapid taken
 Food intake: 3.0 of Starch at 19h20
 Food intake: 1.0 of Protein at 19h20
 Food intake: 0.5 of Milk at 21h50
 Food intake: 1.0 of Fruit at 21h50
21h50:Glucose value of  110mg/dl recorded (6.1 mmol/l)
22h05: 10 units of Ultratard taken
```

```
Monday 2nd June 2003
08h10: 10 units of Ultratard taken
09h10:  8 units of Novorapid taken
 Food intake: 1.5 of Starch at 09h20
 Food intake: 1.0 of Milk at 09h20
 Food intake: 0.3 of Fruit at 09h20
 Food intake: 0.3 of Protein at 09h20
12h05:Glucose value of  137mg/dl recorded (7.6 mmol/l)
 Food intake: 1.0 of Starch at 12h10
12h45:  4 units of Actrapid taken
 Food intake: 1.0 of Starch at 13h15
 Food intake: 1.5 of Protein at 13h15
 Food intake: 1.0 of Fruit at 13h15
 Food intake: 1.0 of Starch at 13h35
 Food intake: 1.0 of Fruit at 13h35
16h25:Glucose value of  331mg/dl recorded (18.4 mmol/l)
16h27:  5 units of Actrapid taken
18h46:Glucose value of  300mg/dl recorded (16.7 mmol/l)
19h25:  5 units of Novorapid taken
 Food intake: 1.0 of Fat at 19h50
 Food intake: 3.0 of Starch at 19h50
 Food intake: 1.0 of Protein at 19h50
22h30:Glucose value of   59mg/dl recorded (3.3 mmol/l)
 Food intake: 0.5 of Starch at 22h45
 Food intake: 1.0 of Protein at 22h45
 Food intake: 1.0 of Fruit at 22h45
23h40: 10 units of Ultratard taken

Tuesday 3rd June 2003
08h10: 10 units of Ultratard taken
09h05:  8 units of Novorapid taken
 Food intake: 1.5 of Starch at 09h20
 Food intake: 0.5 of Fat at 09h20
 Food intake: 1.0 of Milk at 09h20
 Food intake: 1.0 of Starch at 11h30
13h14:Glucose value of  143mg/dl recorded (7.9 mmol/l)
14h20:  8 units of Novorapid taken
 Food intake: 3.0 of Starch at 14h30
 Food intake: 2.0 of Protein at 14h30
 Food intake: 2.0 of Fruit at 14h30
```

```
19h45:  8 units of Novorapid taken
 Food intake: 1.0 of Fruit at 20h10
 Food intake: 2.0 of Starch at 20h10
 Food intake: 0.5 of Fat at 20h10
 Food intake: 1.0 of Protein at 20h10
22h36:Glucose value of  157mg/dl recorded (8.7 mmol/l)
 Food intake: 1.0 of Fruit at 23h00
23h10: 10 units of Ultratard taken

Wednesday 4th June 2003
08h00: 10 units of Ultratard taken
08h40:  8 units of Novorapid taken
 Food intake: 1.5 of Starch at 08h45
 Food intake: 1.0 of Milk at 08h45
 Food intake: 1.0 of Starch at 09h45
12h16:Glucose value of  291mg/dl recorded (16.2 mmol/l)
12h19:  8 units of Actrapid taken
13h34:Glucose value of  203mg/dl recorded (11.3 mmol/l)
15h54:Glucose value of  332mg/dl recorded (18.4 mmol/l)
18h09:Glucose value of  219mg/dl recorded (12.2 mmol/l)
22h18:Glucose value of  163mg/dl recorded (9.1 mmol/l)

Thursday 5th June 2003
10h42:Glucose value of  176mg/dl recorded (9.8 mmol/l)
13h49:Glucose value of  120mg/dl recorded (6.7 mmol/l)
22h04:Glucose value of   77mg/dl recorded (4.3 mmol/l)

Friday 6th June 2003
08h00: 10 units of Ultratard taken
09h15:  8 units of Novorapid taken
 Food intake: 1.8 of Starch at 09h15
 Food intake: 1.0 of Milk at 09h15
 Food intake: 0.3 of Fruit at 09h15
 Food intake: 0.5 of Protein at 09h15
13h15:  8 units of Novorapid taken
 Food intake: 3.0 of Starch at 13h30
 Food intake: 1.0 of Protein at 13h30
 Food intake: 2.0 of Fruit at 13h30
17h38:Glucose value of  214mg/dl recorded (11.9 mmol/l)
19h45:  8 units of Novorapid taken
 Food intake: 3.0 of Starch at 20h05
```

```
 Food intake: 1.0 of Fruit at 20h05
 Food intake: 1.0 of Protein at 20h05
 Food intake: 0.5 of Fat at 20h05
22h30: 10 units of Ultratard taken

Saturday 7th June 2003
09h00: 10 units of Ultratard taken
10h45:  8 units of Humalog taken
 Food intake: 1.5 of Starch at 11h00
 Food intake: 1.0 of Milk at 11h00
 Food intake: 0.3 of Fruit at 11h00
13h45:  8 units of Humalog taken
 Food intake: 3.0 of Starch at 14h00
 Food intake: 1.0 of Protein at 14h00
 Food intake: 1.0 of Fruit at 14h00
15h32:Glucose value of  153mg/dl recorded (8.5 mmol/l)

Sunday 8th June 2003
00h00:Glucose value of  126mg/dl recorded (7.0 mmol/l)
12h55: 10 units of Ultratard taken
13h00:  8 units of Humalog taken
 Food intake: 2.5 of Starch at 13h10
 Food intake: 1.0 of Fat at 13h10
 Food intake: 0.7 of Fruit at 13h10
 Food intake: 0.5 of Protein at 13h10
14h22:Glucose value of  163mg/dl recorded (9.1 mmol/l)
15h40:  5 units of Humalog taken
 Food intake: 2.0 of Starch at 16h00
 Food intake: 0.5 of Fat at 16h00
 Food intake: 0.5 of Protein at 16h00
 Food intake: 1.0 of Protein at 16h10
 Food intake: 1.0 of Fruit at 16h10
19h45:  8 units of Humalog taken
 Food intake: 3.0 of Starch at 20h00
 Food intake: 1.0 of Protein at 20h00
 Food intake: 1.0 of Fruit at 20h30
21h24:Glucose value of  213mg/dl recorded (11.8 mmol/l)
22h20: 10 units of Ultratard taken

Monday 9th June 2003
08h33: 10 units of Ultratard taken
```

```
08h36:Glucose value of   74mg/dl recorded (4.1 mmol/l)
 Food intake: 1.0 of Milk at 08h49
 Food intake: 0.5 of Fruit at 09h30
10h45:Glucose value of  135mg/dl recorded (7.5 mmol/l)
13h20:  8 units of Novorapid taken
 Food intake: 3.0 of Starch at 13h30
 Food intake: 1.0 of Protein at 13h30
 Food intake: 2.0 of Fruit at 13h30
17h43:Glucose value of  142mg/dl recorded (7.9 mmol/l)
19h30:  8 units of Humalog taken
 Food intake: 2.0 of Starch at 19h45
 Food intake: 1.0 of Protein at 19h45
 Food intake: 2.0 of Fruit at 19h45
22h55: 10 units of Ultratard taken
 Food intake: 1.5 of Fruit at 23h05

Tuesday 10th June 2003
07h55: 10 units of Ultratard taken
08h40:  8 units of Humalog taken
 Food intake: 1.5 of Starch at 08h45
 Food intake: 1.0 of Milk at 08h45
 Food intake: 0.3 of Fruit at 08h45
 Food intake: 0.5 of Protein at 09h20
 Food intake: 0.3 of Starch at 09h20
09h51:Glucose value of  163mg/dl recorded (9.1 mmol/l)
 Food intake: 1.0 of Starch at 11h40
 Food intake: 1.0 of Starch at 12h05
13h00:  8 units of Actrapid taken
 Food intake: 2.0 of Starch at 13h20
 Food intake: 1.5 of Fruit at 13h20
 Food intake: 1.0 of Protein at 13h20

Wednesday 11th June 2003
08h30:  8 units of Humalog taken
 Food intake: 1.5 of Starch at 08h40
 Food intake: 1.0 of Milk at 08h40
 Food intake: 0.3 of Fruit at 08h40
 Food intake: 1.0 of Starch at 10h00
 Food intake: 1.0 of Starch at 13h00
13h20:  8 units of Novorapid taken
 Food intake: 2.0 of Starch at 13h40
```

```
 Food intake: 2.0 of Fruit at 13h40
 Food intake: 1.0 of Protein at 13h40
17h31:Glucose value of   58mg/dl recorded (3.2 mmol/l)

Thursday 12th June 2003
11h21:Glucose value of  216mg/dl recorded (12.0 mmol/l)
22h20: 10 units of Ultratard taken
22h29:Glucose value of  178mg/dl recorded (9.9 mmol/l)

Friday 13th June 2003
08h10: 10 units of Ultratard taken
08h20:  8 units of Humalog taken
08h20: 10 units of Ultratard taken
 Food intake: 1.5 of Starch at 08h25
 Food intake: 1.0 of Milk at 08h25
 Food intake: 1.0 of Starch at 08h27
08h35:  8 units of Humalog taken
12h20:  4 units of Novorapid taken
19h20:  8 units of Humalog taken
22h00:Glucose value of  265mg/dl recorded (14.7 mmol/l)
23h06:Glucose value of  287mg/dl recorded (15.9 mmol/l)

Saturday 14th June 2003
12h14:Glucose value of  211mg/dl recorded (11.7 mmol/l)
19h19:Glucose value of  113mg/dl recorded (6.3 mmol/l)

Sunday 15th June 2003
00h52:Glucose value of  299mg/dl recorded (16.6 mmol/l)
09h10: 10 units of Humalog taken
12h12:Glucose value of  251mg/dl recorded (13.9 mmol/l)
13h15:  8 units of Humalog taken
19h03:Glucose value of  242mg/dl recorded (13.4 mmol/l)
21h13:Glucose value of   75mg/dl recorded (4.2 mmol/l)
22h10:  8 units of Humalog taken
23h30: 10 units of Ultratard taken

SUMMARY OF BLOOD GLUCOSE READINGS
for period 20030601 to 20030615

from 00h00 to 04h00:
total number of tests= 2
```

```
number of tests with value below 70mg/dl= 0
number of tests with value above200mg/dl= 1
number of tests within range= 1
Average=212.50 (11.8 mmol/l)
Standard Deviation=122.33 (6.8 mmol/l)

from 04h00 to 08h00:
total number of tests= 1
number of tests with value below 70mg/dl= 1
number of tests with value above200mg/dl= 0
number of tests within range= 0
Average=63.00 (3.5 mmol/l)
Standard Deviation=0.00 (0.0 mmol/l)

from 08h00 to 10h30:
total number of tests= 2
number of tests with value below 70mg/dl= 0
number of tests with value above200mg/dl= 0
number of tests within range= 2
Average=118.50 (6.6 mmol/l)
Standard Deviation=62.93 (3.5 mmol/l)

from 10h30 to 13h00:
total number of tests= 7
number of tests with value below 70mg/dl= 0
number of tests with value above200mg/dl= 4
number of tests within range= 3
Average=202.43 (11.2 mmol/l)
Standard Deviation=57.72 (3.2 mmol/l)

from 13h00 to 15h30:
total number of tests= 5
number of tests with value below 70mg/dl= 0
number of tests with value above200mg/dl= 1
number of tests within range= 4
Average=157.40 (8.7 mmol/l)
Standard Deviation=30.48 (1.7 mmol/l)

from 15h30 to 19h00:
total number of tests= 8
number of tests with value below 70mg/dl= 1
```

```
number of tests with value above200mg/dl= 5
number of tests within range= 2
Average=218.63 (12.1 mmol/l)
Standard Deviation=98.64 (5.5 mmol/l)

from 19h00 to 22h00:
total number of tests= 5
number of tests with value below 70mg/dl= 0
number of tests with value above200mg/dl= 2
number of tests within range= 3
Average=150.60 (8.4 mmol/l)
Standard Deviation=72.50 (4.0 mmol/l)

from 22h00 to 23h59:
total number of tests= 7
number of tests with value below 70mg/dl= 1
number of tests with value above200mg/dl= 2
number of tests within range= 4
Average=169.43 (9.4 mmol/l)
Standard Deviation=85.60 (4.8 mmol/l)


Total number of tests=37
Overall Average=178.84 (9.9 mmol/l)
Overall Standard Deviation=78.56 (4.4 mmol/l)
```

Appendix B

Project Proposal

A Mathematical Model for use in Diabetes Control

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October 1986

Introduction

It seems possible that the problem of blood sugar level control in Type I Diabetes could be aided by the use of a mathematical model of the situation. This could then be used in conjunction with a computer in order to obtain more accurate and dynamic control of the blood sugar level.

What is required is the construction of a mathematical model which describes quantitatively the factors which effect the blood sugar level in a diabetic.

If such a system could be developed it, could then be used on a computer in oder to calculate changes in insulin dose, food intake and exercise periods in order to achieve the best possible control over a period of time.

Such a mathematical model may also be useful in the general study of control in diabetes since it could be used to give a more accurate quantititative idea of the situation.

The variables involved are:
i) Blood sugar level
ii) Insulin intake
iii) Food intake
iv) Exercise
v) Other factors, eg. insulin opposing hormones, stress, illness, and such like.

i) and ii) can be very accurately measured, iii) fairly accurately and it should be possible to calculate a reasonable estimate for iv). If there are factors involved in v) which can not be ignored then their effects will have to be investigated and taken into account.

It is then necessary to develop a mathematical model of the situation giving the quantititative effects of ii), iii) and iv) on i).

The basic equation should be of the form:

$$G(t) = \int_0^t G(0) + F(t) - I(t) - E(t)dt$$

where
G(t) is blood sugar level as a function of time
G(0) is the intial blood sugar level
F(t) is the effect of food intake over time on G
I(t) is the effect of insulin over time on G
E(t) is the effect of exercise over time on G

Various constants involved in the equations will be dependent on the individual concerned, since the effect of a given amount of insulin, intake of food, etc. on the level of a person's blood sugar will depend on the physical attributes of the person. The validity of the model would depend on these values remaining fairly constant.

There are two phases involved to implement such a system:

Phase I

The first thing to do is to determine whether it is possible to set up the system so that given the values of initial blood sugar level, food intake, insulin intake and activity levels, it can extrapolate the blood sugar level over a period of

time.

The functions for F(t), I(t) and E(t) can be represented by polynomials. (They can be approximated by interpolative polynomials.)

Let us assume that interpolative polynomials of order 2 are sufficient.

Thus:

$$F_n(t) = a_{n;2}t^2 + a_{n;1}t + a_{n;0} 0 < t < t_{a;n}$$

$$E(t) = -k(b_2t^2 + b_1t + b_0) 0 < t < t_b$$

$$I_i(t,k) = -(c_{i;2}t^2 + c_{i;1}t + c_{i;0}) 0 < t < t_{c;i}$$

where:

F_n is the function for the n^{th} food item

I_i is the function for the i^{th} type of insulin (fast, medium of slow acting)

k is the level of exercise

$I(t,k)$ includes the exercise level factor (k) since it is known that insulin absorption rate is affected by physical activity due to increased blood flow during periods of exercise.

In order for the model to be useful the error levels of the calculations will have to be small enough to keep the calculated values within acceptable ranges.

Keeping blood sugar values between 100 and 200 mg/dl is considered to be reasonable control. Thus, for example, (don't take these figures too seriously!) if a value of 130 mg/dl is aimed for, and the error bound is 25 mg/dl, then values in the range 105 - 155 mg/dl can be expected to be maintained. The point here is that although extrapolated values can by no means be expected to be exact, the bounds for the error levels do not have to be all that small for the model to be useful.

It should also be possible to deduce from such a model the periods during the day/night during which the blood sugar levels are likely to deviate from levels which are considered to be acceptable.

Phase II

If Phase I can be successfully completed, the next step is to develop a program to implement the system on a computer. With so many variables involved, in order to have a manageable situation most of the variables will have to be held constant and the best values for the others calculated.

A reasonable way may be to keep F and E at predetermined values, and then calculate the best doses of insulin to produce an I curve which will give optimal control. Along with proposed values for F and E over the period concerned, restrictions for the calculations of doses could be input, such as the periods during which they could be given, and the maximum permissable number of injections allowed within a period, thus further limiting the number of free variables which need to be calculated, and giving the users a reasonable amount of control over the recommended doses of insulin.

Once the program has been developed it could then be run on almost any computer (restrictions being the amount of memory required, and perhaps the processing time required).

It is also possible that it could be built into a dedicated machine (hardwired with the program in ROM). Such a machine should be less expensive than a normal microcomputer. This kind of machine could be something like the present day blood glucose testing machines.